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JANUARY, 1940

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ORIGINAL ARTICLES.

THE NATURE OF THE HEMORRHAGIC DISEASE OF THE  
NEWBORN.

DELAYED RESTORATION OF THE PROTHROMBIN LEVEL.

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KNOWLEDGE concerning the danger of hemorrhage in the newborn dates back to ancient times. In Genesis one finds the Mosaic law specifically setting the eighth day after birth as the time for circumcision, and numerous repetitions of this law are found both in the Old and New Testament. Even now circumcision and other operations are usually postponed until the baby is a week old. Nevertheless, this potential danger of hemorrhage is not clearly and generally recognized since excessive bleeding is relatively rare. When hemorrhage does occur in babies, it is usually looked upon as a distinct clinical entity to which has been given the name "hemorrhagic disease of the newborn."

The existence of a bleeding disease in newborn infants was first reported in the European literature by Mauriceau<sup>16</sup> in 1682. Umbilical bleeding was reported by Watts<sup>31</sup> in 1753, and Cheyne<sup>6</sup> recorded a case in 1801. The disease was also described in a treatise by Capuron<sup>5</sup> in 1820. H. J. Bowditch,<sup>2</sup> apparently the first American



who published studies of the hemorrhagic disease in babies, recognized the possibility that umbilical bleeding was perhaps only one manifestation of a hemorrhagic diathesis. F. Minot<sup>17</sup> presented a similar view in a paper published 2 years later, and suggested that jaundice might be an etiologic factor as he found a frequent association of bleeding with icterus. The concept that umbilical bleeding was a part of a more general bleeding tendency was further established by the work of Coale<sup>8</sup> and Thayer.<sup>26</sup> In 1894 appeared the classical paper of Townsend,<sup>27</sup> in which he named the syndrome "the hemorrhagic disease of the newborn." He furthermore clearly differentiated this condition from hemophilia and emphasized the fact that the disease was self-limited. He believed that infection was the cause. The further minor developments in the recognition of this disease have been adequately summarized by Gelston,<sup>9</sup> and Lövegren<sup>13</sup> has reviewed the literature on melæna neonatorum.

The cause of the hemorrhagic disease in newborn babies baffled the early investigators, and little that was in any way helpful in determining the basic factors responsible for the bleeding was contributed by subsequent workers. Minot listed as possible etiologic factors: hereditary predisposition, sex, liver dysfunction, and imperfect closure of the umbilical vessels. Townsend, as already mentioned, considered the disease of infectious origin. In 1912, Schloss<sup>23</sup> summarized the prevailing views of the disease. He pointed out that the bleeding may be due to hemophilia, infection, congenital syphilis, gastric or duodenal ulcers, a defect in the coagulation mechanism such as a deficiency of fibrinogen, diminution of thrombin, or to localized vascular lesions. Schloss and Commiskey<sup>24a</sup> somewhat earlier had reported that in the hemorrhagic condition of the newborn, coagulation may be normal, delayed, or absent. In retrospect, the most important observation was that of Whipple<sup>23</sup> who found a complete absence of prothrombin in a fatal case of this disease. Unfortunately, the test was made on postmortem blood. Furthermore, knowledge concerning the coagulation mechanism was in such a confused state at that time that his findings could not be properly evaluated.

In 1921 Rodda<sup>21</sup> made the interesting observation that the coagulation time of babies had a tendency to increase after birth, reaching the maximum retardation on the fifth day, but returning to normal before the tenth day. Lucas and his associates<sup>14</sup> confirmed these observations. No satisfactory explanation for these findings could be offered. Sanford and Leslie<sup>22</sup> came to the conclusion that the platelets were more resistant to disintegration in this hemorrhagic disease.

Since the cause of the hemorrhage in infants was not known, treatment could not be specific. Minot and the other early investigators attempted merely to treat the bleeding locally with styptics and astringent agents. The injection of gelatin solution was used,

especially by European clinicians.<sup>13</sup> In 1908 Lambert<sup>12</sup> successfully treated a bleeding baby with a direct transfusion of blood. Welch<sup>32</sup> a little later reported a series of 12 cases treated both by direct transfusion and by subcutaneous injection of blood. Schloss and Commiskey<sup>24a</sup> introduced the method of injecting small amounts of blood intramuscularly. The authors, however, recognized the difficulty of evaluating the efficacy of this treatment because of the fact that spontaneous recovery could occur. In fact, they reported in a later paper<sup>24b</sup> a case in which the baby died in spite of the treatment with several injections of blood. Soresi<sup>25</sup> advocated direct transfusion as the best method. Nevertheless, the injection of whole blood intramuscularly became a widely accepted therapeutic measure. Sanford and Leslie recently challenged the value of this method and advocated intravenous transfusion as the preferred means of giving blood.

With the recognition of the importance of prothrombin deficiency as a cause of hemorrhage, and the discovery that vitamin K is essential for the synthesis of this clotting factor, came a new approach to the study of hemorrhagic disease of the newborn. In 1935 Quick<sup>19a</sup> described a quantitative method for prothrombin and showed that this clotting agent was markedly diminished in certain jaundiced patients. A year later Warner, Brinkhous and Smith<sup>29</sup> adopted the principle of Quick of adding an excess of thromboplastin and developed a second method for determining prothrombin. Instead of completing the test in one step, they determine the dilution of the plasma which with thromboplastin and calcium will clot a solution of fibrinogen in 15 seconds, and they express the concentration of prothrombin in terms of this dilution factor. By means of their method, Smith and his associates<sup>3</sup> found almost a complete absence of prothrombin in a case of severe bleeding that occurred in a newborn infant, which confirmed the earlier observation of Whipple. Oddly, however, when they applied their method to the study of normal infants' blood, they found astonishingly low values. In 4 babies, 5, 8, 8, and 11 days old, the prothrombin concentration was 36, 44, 27 and 37% respectively, and even babies 2 months old still had a prothrombin level of only 42% of normal. These results suggest that all babies are in potential danger of hemorrhage during the first few weeks of life, which is not in accord with clinical observations.

Since the methods of both Smith and his associates, and of Quick are based on unproved assumptions, it is possible to evaluate them only in terms of their correlation with clinical and experimental findings. In regard to Quick's method, it has been found to be a delicate measure of the prothrombin concentration in the blood of jaundiced patients and promptly shows the response to vitamin K therapy.<sup>19d</sup> Likewise in experimental studies of vitamin K deficiency in chicks<sup>19b</sup> and in rats<sup>10</sup> the procedure showed a progressive

drop of prothrombin, and a restoration to normal when the vitamin was supplied. In chloroform poisoning in dogs, a severe fall in prothrombin was also found with this method.<sup>19c</sup> In sweet clover disease<sup>19b</sup> the method demonstrated the continuous drop in prothrombin, and the accuracy of the determination was shown by the fact that when the prothrombin reached a certain level the animal invariably died from a hemopericardium if blood was taken by heart puncture. Recently the method was employed to demonstrate prothrombin deficiency in various intestinal disorders and to show the response to vitamin K therapy.<sup>4</sup> Thus, the method of Quick has given satisfactory results in the study of all hemorrhagic diseases characterized by a deficiency of prothrombin. In many conditions, moreover, this method yields results which run parallel with those obtained with Smith's procedure. It seemed therefore desirable to study the prothrombin concentration of the blood of newborns with Quick's method.

TABLE 1.—QUANTITATIVE DETERMINATION OF PROTHROMBIN.  
Clotting time.\*

Concentration of prothrombin in plasma, %.	Undiluted plasma, sec.	Diluted plasma,† 50%, sec.
100 . . . . .	11-12	15
97 . . . . .	..	15½
90 . . . . .	..	16
85 . . . . .	..	16½
80 . . . . .	12½	17
75 . . . . .	..	17½
70 . . . . .	..	18
67 . . . . .	..	18½
65 . . . . .	..	19
60 . . . . .	13½	19½
58 . . . . .	..	20
56 . . . . .	..	20½
53 . . . . .	..	21
50 . . . . .	15	21½
40 . . . . .	17	
30 . . . . .	19½	
25 . . . . .	22	
20 . . . . .	25-26	
10 . . . . .	37-40	
5 . . . . .	55-65	

\* Oxalated plasma, 0.1 cc., is mixed with 0.1 cc. of thromboplastin solution, and recalcified with 0.1 cc. of 0.025 M calcium chloride. The clotting time is determined at 37.5° C.

† The plasma is diluted with an equal volume of physiologic saline solution.

**Procedure.** Blood was drawn from the internal jugular vein. Usually 1.8 cc. of blood were taken and mixed immediately with 0.2 cc. of 0.1 M sodium oxalate. The plasma was analyzed for the prothrombin content by the method described previously.<sup>19c</sup> Since the variations in clotting time between 50 and 100% are very small, greater accuracy is obtained by diluting the plasma with an equal volume of physiologic saline solution, and then determining the clotting time of the 50% plasma (Table 1).

It has been found that if the thromboplastin which is prepared by the acetone method is kept in evacuated glass ampules, no loss of activity occurs.

**Results.** The results are summarized in Chart 1. At birth the concentration of prothrombin is relatively high, about 60 to 75% of the normal adult value. The series, however, is too small to conclude that the prothrombin is nearly normal in all newborn infants, but the fact that the analysis of a great number of cord bloods (placental) gave values of 60 to 70% suggests that the prothrombin in the baby at birth is fairly high. Soon after birth, however, the prothrombin decreases, and may reach exceedingly low levels. In the babies studied, the prothrombin was lowest the first day, somewhat higher during the second day, and almost always normal after the third day. Since these results were first reported,<sup>20</sup> Waddell and Guerry,<sup>28</sup> and Owen, Hoffman, Ziffren and Smith<sup>18</sup>

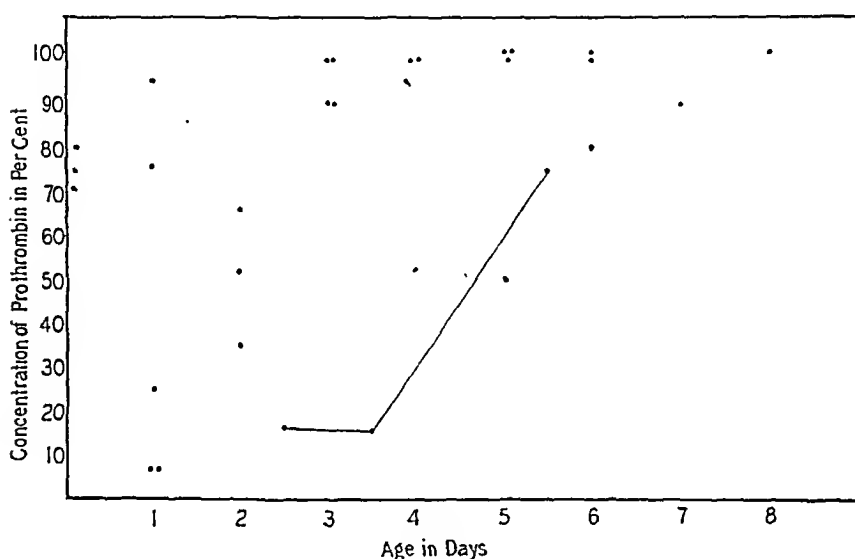


CHART 1.—The prothrombin concentration in the blood of newborn infants. All babies were in good health. One baby with a prothrombin of 7% had mild umbilical bleeding. The points connected by lines show the restoration of the prothrombin in one infant.

(both groups using Quick's method) obtained similar results with the exception that the drop in prothrombin usually came on the second and third days and returned to normal after the fifth day.

From the results obtained, it can be concluded that at birth the prothrombin in the baby's blood is relatively high, but often drops precipitously during the first days of life, and then, strangely, is spontaneously restored. Immediately, an answer is suggested to the question of the origin of the hemorrhagic disease of the newborn. The frequency with which the prothrombin falls in normal infants makes it highly probable that all infants are in danger of hemorrhage during the first few days of life. In the recognized hemorrhagic disease of the newborn, it is very likely that the fundamental cause is a delay in the spontaneous restoration of the prothrombin level. It

will be recalled that Townsend in 1894 clearly stated that the disease was self-limited. Thus, it seems that the hemorrhagic disease of the newborn is a potential threat to all infants. Consequently, if an infant should bleed accidentally, the small loss of blood may be sufficient to reduce the prothrombin level which is already low to a point where hemorrhage becomes difficult to control, and a vicious circle is initiated.

The cause of the prothrombin deficiency seems to be due to an inadequate storage of prothrombin or of vitamin K in the fetus. Presumably as soon as the baby is born, the physiologic demands promptly exhaust the available prothrombin. Since there is apparently neither a reserve of vitamin K nor of prothrombin, a marked decrease of the latter occurs. The condition is clearly due to a lack of vitamin K, for not only can the prothrombin be promptly restored to normal by giving the baby a concentrate of this vitamin, but also the serious fall in concentration can be prevented by the oral administration of this food accessory substance.<sup>28</sup>

This leads to the interesting speculation concerning the spontaneous recovery of the prothrombin level in normal infants. Since the drop in prothrombin is distinctly a manifestation of vitamin K deficiency, the rise must be due to a supply of this vitamin which was not present at birth. In view of the fact that the food intake during the first few days is scarcely sufficient to assure an adequate supply of vitamin K, another source must be sought. As is well known, especially from Almquist's<sup>1</sup> work, bacteria readily synthesize vitamin K. At birth the intestinal contents of the baby are sterile, but in a very short time, especially if the baby is allowed to suckle, bacteria are introduced, and an intestinal flora is established. The time relation between the beginning of bacterial activity and the restoration of the prothrombin level makes it appear likely that the available vitamin K is of bacterial origin. This explains adequately the rather puzzling finding of Javert<sup>11</sup> that the incidence of hemorrhagic disease of the newborn in a large series of cases was over twice as high in the New York Hospital as in the outdoor service of the Berwind Free Maternity Clinic. The babies born under the far less sanitary conditions of the home or tenement had a chance to infect their intestinal tracts sooner than the babies born under the ideal conditions of a modern hospital. Perhaps the practice of putting the baby to the breast early serves the primary purpose of introducing harmless but useful bacteria into the alimentary tract.

While one can only speculate on the cause of the fall of prothrombin and its rather prompt restoration in normal infants, the fact seems well established that even a healthy infant with no visible signs or symptoms may have for a short period an astonishingly low concentration of prothrombin in its blood. With this concept, a concise delineation of the hemorrhagic disease of the newborn can now be presented. Only a few months ago Clifford<sup>7</sup> wrote: "The

diagnosis of hemorrhagic disease can only be made on clinical grounds until its etiology is established, in the absence of characteristic pathology or consistent laboratory findings." Now the diagnosis can be made by laboratory means, before the child shows clinical signs, and the chief etiologic factor can be considered as a deficiency of prothrombin due to absence of vitamin K. The conclusion of Clifford that the hemorrhagic disease is a loose clinical syndrome and not a true disease entity no longer holds and the confusion concerning the disease, which this author discusses at length, can be cleared.

The hemorrhagic disease of the newborn is clinically recognized by external or internal hemorrhage occurring during the first few days of life; is characterized by an exceedingly low prothrombin content of the blood; is usually self-limited but may be fatal; and is promptly cured by vitamin K. It is probable that the disease may be precipitated by a small hemorrhage, thus further reducing the depleted prothrombin as already discussed. Although no positive proof exists that cerebral hemorrhage in babies following delivery is one form of the "hemorrhagic disease," it seems very likely that it is, and that the lowered prothrombin is the important factor. If the latter clotting agent were normal in amount, the excess of thromboplastin which is present in the brain would speedily stop hemorrhage.

With these considerations, attention can be turned to the prevention and treatment of the disease. Since no evidence exists that the baby is born with a marked deficiency of prothrombin, the important problem to be solved is the prevention of the fall in the clotting factor. Waddell and Guerry have demonstrated that this can be accomplished by administering vitamin K orally. But in the normal infant, this hardly seems necessary. Perhaps a return to the practice of early breast feeding will be sufficient. But in any case of difficult labor in which intracranial injury is likely to occur, the oral administration of a concentrate of vitamin K should begin immediately and be continued for several days. Vitamin K should also be given promptly if slight oozing is noticed from the umbilical cord or any other small wound, or if blood appears in the stool or urine. Unless the hemorrhage is severe, a direct blood transfusion need not be given since vitamin K acts very promptly. Whether intramuscular injection of blood is of any value has never been satisfactorily answered.

Jaundice in the newborn is not a contributing factor, for a number of babies who were distinctly icteric had a normal prothrombin level, whereas babies that had shown a low prothrombin level had no evidence of bile in the blood. Furthermore, a case with congenital atresia of the common bile duct reported earlier<sup>19c</sup> showed a normal prothrombin, and another baby 5 weeks old that was jaundiced from birth likewise had a concentration of 100% normal. Watkins and Wright<sup>30</sup> found that a baby who survived 15 months with

congenital atresia of the bile duct had a normal coagulation time. It appears that when the normal prothrombin level is once established in the baby, it becomes difficult to cause any appreciable diminution. It is therefore usually possible to operate on a child after it is a week old without danger of untoward bleeding. If it is imperative that an operation be performed earlier, the prothrombin should be determined by Quick's method, and if it is found low, vitamin K should be given preoperatively.

With this new concept of the hemorrhagic disease of the newborn, rapid progress can be expected. The prevention of the prothrombin decrease after birth is of particular importance and warrants further study. While it appears likely that the vast majority of bleeding cases will be found to be due to prothrombin deficiency, it must be recognized that other types of hemorrhagic diatheses may be encountered. Congenital absence of fibrinogen, although exceedingly rare, can be the cause of bleeding.<sup>15</sup> Hemophilia, perhaps, rarely manifests itself immediately after birth, but theoretically must be considered. It is interesting that the 2 cases reported by Bowditch are not altogether typical of hemorrhagic disease of the newborn, as this clinical entity is now recognized. In his cases, the hereditary factor seemed most important. According to present concepts, a definite diagnosis can only be made by establishing a low prothrombin by laboratory tests, or by curing the disease with vitamin K. If these two diagnostic tests are negative when applied to an unknown bleeding condition, it does not belong to the disease presented in this paper.

**Summary.** It has been found that the prothrombin concentration of infants' blood is nearly at the same level at birth as that of the adult. It often drops, however, abruptly during the first few days of life, but is restored spontaneously and usually promptly to normal. The suggestion is made that the recovery of the prothrombin concentration is brought about by the establishment of a bacterial flora in the intestines, and that this initiates the synthesis of vitamin K which becomes available to the organism of the infant for the production of prothrombin.

The hypothesis is presented that the cause of the hemorrhagic disease of the newborn is due to a delayed restoration of the prothrombin level, and the disease is defined as one which is clinically recognized by external or internal bleeding; is characterized by an exceedingly low prothrombin concentration in the blood (as determined by the method of Quick); is usually self-limited, but may be fatal; and is promptly cured by the oral administration of vitamin K.

Since this paper was submitted, Nygaard (*Acta Obst. et Gyn. Scand.*, 29, 361, 1939) reported that the prothrombin is normal at birth but begins to drop during the second half of the first day. He further reports that vitamin K prevents this fall in prothrombin. Three cases of bleeding in the newborn responded promptly to vitamin K given orally.

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## BLOOD STUDIES ON THE NEWBORN.

## II. DIRECT AND TOTAL BLOOD BILIRUBIN: DETERMINATIONS OVER A NINE-DAY PERIOD, WITH SPECIAL REFERENCE TO ICTERUS NEONATORUM.

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In a previous communication<sup>31</sup> the authors have reported changes in the hemoglobin, volume of packed red cells, reticulocytes, and fragility of the erythrocytes in a series of newborn infants over a 9-day period. At the same time investigations were carried out



on the changes in the bilirubin content of the blood plasma, utilizing the Evelyn<sup>7,8</sup> photoelectric colorimeter technique. The present paper is concerned with this phase of our research. Before presenting this, however, we believe it would be advisable to review briefly some of the more pertinent facts in regard to bilirubin and some of the recent advances in our knowledge.

It is now generally accepted that bilirubin and hematoidin are chemically identical and that the hemoglobin liberated from the destruction of red cells is the only known source of bilirubin.<sup>2,24a</sup> The direct and indirect Van den Bergh reactions of bilirubin with the diazo reagent are familiar to everyone, but there has been considerable debate as to the nature of these reactions. Two theories have arisen: 1, that the two types are chemically identical but that in the indirect form the bilirubin is adsorbed by a serum constituent (apparently globulin) and so prevented from reacting directly with the diazo; 2, that there is a difference in chemical composition between the bilirubin normally found in the circulating blood and that which has passed through the liver cells. The experiments of Bollman, Sheard and Mann<sup>3</sup> lent considerable support to the first when they showed that alcohol-acetone and aqueous solutions of serum from cases with obstructive and hemolytic jaundice when measured spectrophotometrically gave similar light transmission curves. Barron<sup>2</sup> demonstrated *in vitro* that direct reacting bilirubin when added to normal serum was transformed into the indirect type, and that the addition of a substance of lower surface tension (which would be more readily adsorbed, thus freeing the bilirubin) such as alcohol, bile salts or cholesterol, brought about a reversal to the original form. The application of this to the function of the liver is apparent. In support of the second theory, Andrewes<sup>1</sup> observed that the direct reacting bilirubin oxidizes more easily than the indirect type. Van den Bergh<sup>30</sup> pointed out that the direct bilirubin is more readily adsorbed by the protein precipitate formed by the addition of alcohol to sera than is the indirect bilirubin, while Grunnenberg<sup>12</sup> found that the direct reacting bilirubin passes into solution with chloroform while the indirect does not. Others have supported one or the other of these concepts, but it is without the scope of this paper to review the literature completely.

With the qualitative and comparatively crude quantitative Van den Bergh methods which have been used in the past, the distinction between the various types of bilirubin reaction was apparently sharp. This led to their usage for diagnostic purposes which, while of distinct clinical value, has unfortunately brought about erroneous conclusions concerning the types of bilirubin as they exist in the blood. This has been well demonstrated by the work of Malloy and Evelyn,<sup>21a</sup> employing the photoelectric colorimeter, which has shown that even in the blood of normal adults from 35 to 70% of

the total bilirubin is the direct type, the remainder being the indirect. By studying the various types of icterus they have found that there are always direct and indirect components of the total bilirubin which exist in varying percentages of the whole, depending upon the pathogenesis of the condition. For example, in jaundice due to biliary obstruction the direct percentage will be 60 to 80% or more of the total, but there will always be a small percentage of the indirect, while in hemolytic jaundice the values for the two forms will be reversed. In other words, the quantitative differences between direct and indirect bilirubin become a more or less relative matter. This would seem to support the view that the differences in relative amounts of the direct and indirect reacting bilirubin material are dependent upon some adsorptive substance which is present in the blood at all times to a slight degree but reaches high figures in the regurgitative (obstructive) types of jaundice.

Icterus neonatorum simplex has been accepted as a normal physiologic process in the readjustment of the infant to extra-uterine life, but there has never been complete unanimity of opinion as to the pathogenesis. Jaundice in the newborn, of course, may be caused by other factors, such as congenital malformations of the bile ducts, sepsis, congenital syphilis, erythroblastosis, and so forth, but we are not primarily concerned here with these. It has been customary in the past to distinguish between icteric and non-icteric infants, although it has been known for some time that all infants show a hyperbilirubinemia at birth, and that this bilirubin reacts indirectly with the diazo reagent.<sup>16,19,23a,29,33</sup> Therefore, the terms icteric and non-icteric refer purely to the objective outward signs of jaundice. The incidence of icterus neonatorum has been variously reported from 30 to 90% or more, according to the criteria laid down for diagnosis.

It is generally agreed that there occurs an increased blood destruction in the newborn which leads to the formation of an excessive amount of bilirubin and which results in a certain degree of hyperbilirubinemia. It is a controversial point, however, in those cases in which the hyperbilirubinemia reaches a level sufficient to cause jaundice, whether this is due primarily to an excessive amount of blood destruction, or whether it is the result of an inability of the liver cells to excrete the bilirubin which has been brought to them, thus resulting in an increasing retention of bilirubin during the first 4 to 7 days of life.

Among the considerations supporting the theory that excessive blood destruction alone is sufficient to explain the jaundice are the observations of Gordon and Kemelhor,<sup>10</sup> Greil,<sup>11</sup> Rolleston and McNee,<sup>25</sup> and others, who found the presence of icterus and the degree of hyperbilirubinemia proportional to the rate of excessive blood destruction as noted by reduction of the red cells and hemoglobin. The hemolytic nature of the icterus was assumed by

Lepehne<sup>17</sup> and others on the basis of the constant indirect reaction of the bilirubin in the absence of the direct reaction. Goldbloom and Gottlieb<sup>5a</sup> attributed the initial polycythemia to the low oxygen tension of the fetal blood, and using guinea pigs showed that increasing the oxygen tension brought about an increased blood destruction and a rise in blood bilirubin. Further, they reported<sup>9b</sup> an increased fragility of the red cells associated with a fall in immature cells. Therefore, from these and the above observations, they concluded that icterus neonatorum was a hemolytic icterus and was the result of a postnatal readjustment from a condition of oxygen unsaturation to one of normal oxygen saturation. Ehrenfest,<sup>5</sup> Schwartz, Baer and Weiser,<sup>28</sup> and others attributed icterus to increased blood destruction on the basis of birth trauma and hemorrhage. Book<sup>4</sup> observed that ligation of the cord before cessation of pulsation reduced the incidence and degree of jaundice, and believed it due to the elimination of about 100 cc. of blood from the circulation. Williamson<sup>32</sup> noted that blood pigment was deposited in the placenta and supported the theory by observing a relationship between icterus and the height of placental iron deposits. Others have lent support to this theory but space does not permit a complete review of the literature.

The second theory, or that of primary liver insufficiency as the essential difference in the icteric and non-icteric infants, has gained considerable support from the observations of McMaster and Rous<sup>20</sup> who showed the normal liver to have a tremendous reserve capacity, so that even a small amount of normal tissue was capable of preventing jaundice in the presence of increased amounts of bilirubin. Rich<sup>24b</sup> doubted if an uncomplicated excessive production of bilirubin was ever the cause of jaundice, and attributed icterus neonatorum to increased bilirubin formation and an impaired function of the liver cells due to immaturity. The physiologic insufficiency of the liver of the newborn was advocated by Yllpo,<sup>33</sup> and Hirsch<sup>16</sup> on the basis of functional immaturity, and they showed by comparative studies of icteric and non-icteric infants that the total excretion of bile pigments in the urine and stool was similar in the two groups, and further, that there was no agreement between the degree of icterus and the total amount of pigment excreted. Hess,<sup>14</sup> Snelling,<sup>29</sup> and Yllpo<sup>33</sup> observed a low initial bilirubin excretion which was followed later by an increased output at a time when the blood bilirubin was falling. Then Ross, Waugh and Malloy<sup>27</sup> showed that in the cases with jaundice the average total excretion of urobilin in the stool and urine was lower than in those without jaundice, which was contrary to what one would expect in a purely hemolytic icterus. On the other hand, it was noted that an appreciable amount of bilirubin was present in the urine of only the icteric group, and they concluded that the liver cells of the jaundiced infants have a temporary functional inability to excrete bile pigment

in sufficient quantity. Levulose tolerance tests by Heynemann<sup>16</sup> and bromsulphonephthalein excretion tests by Herlitz<sup>13</sup> clearly indicated reduced liver function on the part of all infants, as have the observations that jaundice is more frequent in prematures.<sup>18</sup> Snelling<sup>29</sup> advocated liver insufficiency on the basis of interference of normal function by a persistence of hematopoietic activity of the liver which lasted for several days. Elton<sup>6</sup> returned to the original theory of Quincke, to postulate a patent ductus venosus as the cause of the hyperbilirubinemia and jaundice. Grossly, he could find no relationship between blood changes and the intensity of jaundice or the degree of hyperbilirubinemia—a fact which has been mentioned by others.<sup>19, 23b, 29</sup> Working with dogs, Meier<sup>22</sup> was unable to increase the normal icterus neonatorum by the injection of phenylhydrazine and concluded that insufficiency of the liver rather than blood destruction was the primary factor.

It is apparent, therefore, that there is considerable evidence supporting both the hemolytic and hepatic hypotheses. It would seem, however, if it could be demonstrated by the more precise and detailed methods now available that no relation was found to exist between the amount of blood destruction and the development of icterus neonatorum, then the former theory would have to be set aside. With the material from our studies on newborn infants, it seemed quite possible that this might be done.

**Source of Material.** The newborn infants studied in this work are the same individuals reported previously<sup>31</sup> and are normal full-term infants born on the wards of the maternity unit of the Royal Victoria Hospital. We limited our study to a 9-day period, making determinations on the day of birth (cord blood), second, fourth, sixth and ninth days. The cord blood was obtained usually after cessation of pulsation in the cord. Thereafter, the blood was obtained from the sagittal sinus by fontanel puncture. The infants were closely observed on the ward in order to detect the occurrence of icterus neonatorum, erythroblastosis, complications and so on. We examined 65 newborns, obtaining complete 5-day studies on 33, 4 out of 5 on 12, and 3 or less on the remainder, with 5 disqualified because of illness or transfer. In all, we carried out over 250 examinations. No attempt is anticipated to follow these infants in the outpatient department.

**Technique.** Throughout this study we have utilized the Evelyn photoelectric colorimeter<sup>7, 8</sup> and a modification of the technique for bilirubin determinations developed by Malloy and Evelyn.<sup>21b</sup> The colorimeter is a stabilized, direct-reading, single photocell, photoelectric colorimeter equipped with light filters. The filter with a maximum transmission of 540 millimicrons was used because light which has passed through it is readily absorbed by solutions of azobilirubin, and further it is unaffected by the yellow serum pigments, the absorption of which is negligible at this transmission. Hemoglobin, of course, as we noted in our first paper, does absorb light through this filter, but any error from this source (unless there is very marked hemolysis) is obviated by the use of a blank tube in the initial adjustment of the instrument. The technique utilizes a high concentration of alcohol (approx. 50%) so that all of the bilirubin reacts with the diazo reagent even in the presence of serum proteins. However, the method eliminates protein precipitation by means of an initial dilution with

water, hence any loss of bilirubin caused by adsorption on the protein precipitate is eliminated. Malloy and Evelyn have been able to recover within 2% of all the bilirubin in serum and other media, and thus the method gives higher and more accurate values than any other method heretofore employed. Our procedure is as follows:

Reagents: 1. Diazo reagent—freshly prepared by adding 0.3 cc. of Ehrlich's solution\* No. 2 to 10 cc. of Ehrlich's No. 1. In our modification we used 60% dilutions of the Ehrlich solutions. 2. Diazo blank—9 cc. of concentrated HCl diluted to 1 liter with distilled water. 3. Absolute methyl alcohol.

Procedure: Two colorimeter tubes are set up and into each 5 cc. of a 1 to 20 dilution of plasma is placed. To one tube 1 cc. of the diazo reagent is added, while to the other 1 cc. of the diazo blank is added. The colorimeter is adjusted with the blank tube, then the sample tube is placed in the instrument and read at the end of 10 minutes and again at the end of 30 minutes. The amount of direct bilirubin is then calculated from a prepared table,<sup>21b</sup> the figure from which is divided by 7 to give the final result because of the dilution of our solution. To determine the amount of total bilirubin present in the plasma, 6 cc. of absolute methyl alcohol are then added to each tube and gently mixed. After 15 minutes, the colorimeter is again adjusted with the blank tube, then the sample read. The total bilirubin is then calculated in the same manner as above, but the final result is obtained by dividing by 3.5.

By this method we determine the direct and total bilirubin in plasma, rather than the direct and indirect reacting bilirubin. The difference between the two is, of course, the amount of indirect present. It has been found that an adult will normally have a total bilirubin of 0.2 to 0.8 mg. %, of which about 35 to 70% is of the direct type.

*Total Bilirubin.* We found the average total bilirubin in the cord blood of 53 infants to be 1.35 mg. % with a dispersion of 0.54 to 1.98 mg. %. The average total bilirubin on the second-day venous blood of 48 infants was 3.17 mg. % (0.33 to 5.94 mg. %), while it was 5.27 mg. % (0.57 to 11 mg. %) in 47 newborns on the fourth day, 4.21 mg. % (0.19 to 13 mg. %) in 41 infants on the sixth day, and 3.1 mg. % (0.32 to 9.3 mg. %) in 41 infants on the ninth day. In our series, 30% of the cases developed icterus neonatorum. Of these 18 infants, all but 5 became jaundiced on the fourth day, the others developing it on the second, third and fifth days (see Table 1).

TABLE 1.—COMPARISON OF TOTAL AND DIRECT BLOOD BILIRUBIN, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY BETWEEN ICTERIC AND NON-ICTERIC INFANTS DURING THE PERIOD STUDIED.

Day.	Total bilirubin, mg. %.		Direct bilirubin, mg. %.		Hemoglobin, gm./100 cc.		Vol. packed red cells, %.		Index of fragility.	
	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.
Cord blood . . .	1.39	1.31	0.49	0.53	15.07	15.49	51.1	51.4	390	405
2d day . . .	3.52	2.82	0.51	0.51	15.4	15.54	48.8	49.8	338	350
4th day . . .	6.32	4.22	0.49	0.44	15.3	15.52	47.7	49.2	335	324
6th day . . .	5.67	3.48	0.49	0.53	14.5	15.13	45.1	47.7	346	333
9th day . . .	4.07	2.13	0.53	0.48	14.35	14.85	44.4	46.5	379	344

\* Ehrlich's solution No. 1 is prepared by 1 gm. of sulphanilic acid dissolved in 15 cc. concentrated HCl and diluted to 1 liter with water. Ehrlich's solution No. 2 is 0.5% sodium nitrite.

It will be observed that the two groups show the same average total bilirubin in the cord blood, but that the icteric infants have a slightly higher concentration of the pigment on the days examined thereafter. On closer inspection of the individual cases, however, a wide variation in values within the two groups was found. It was noted on the fourth day, when the majority were jaundiced and the values for almost all infants were at a maximum, that of the 15 icteric infants, 12 had a total bilirubin greater than 5 mg.%, while only 3 were less—the lowest being 0.73 mg.%. Of the 32 non-icteric infants, 20 had values less than 5 mg.%, while the remaining 12 showed values greater than this—the highest being 8.1 mg. %.

We feel, therefore, that there is no strict proportion between the presence of visible jaundice and the degree of hyperbilirubinemia, although as would be expected a rough relationship is found and icterus neonatorum for the most part varies only in degree, with 5 mg.% of total bilirubin the approximate threshold for visible jaundice. It should be pointed out that the discrepancies which exist are undoubtedly explained by the frequent difficulty in recognizing slight degrees of jaundice in the presence of racial variations of normal skin coloring and by the differences of opinion on the part of observers. Or, as Ross, Waugh and Malloy<sup>27</sup> suggest, it may be due to a variable affinity of certain tissues in individual infants for bile pigment.

It is interesting to note that all children are apparently born with a quantity of total blood bilirubin which would be regarded as a hyperbilirubinemia in the adult. The cord blood of several pre-matures was observed to show a similar picture.\* It seems probable, therefore, that a state of hyperbilirubinemia exists in the fetus at least through the latter months of gestation, and that this state is due to some factor other than the postnatal blood destruction. These cord blood values, however, are low as compared with the hyperbilirubinemia which subsequently develops in the vast majority of the cases.

*Direct Bilirubin.* We demonstrated a constant quantity of the direct diazo reacting bilirubin during the period studied. The cord blood averages of 51 infants was 0.51 mg.% with a dispersion of 0.06 to 0.94 mg.%. On the second-day venous blood, the average of 48 cases was 0.51 mg.% (0.09 to 1.26 mg.%), while it was 0.46 mg.% (0.13 to 0.79 mg.%) for 47 cases on the fourth day, 0.51 mg.% (0.06 to 1.01 mg.%) for 41 infants on the sixth day, and 0.51 mg.% (0.16 to 0.86 mg.%) for 41 infants on the ninth day (see Table 1). It will be observed that the averages are approximately the same throughout the period for both groups.

The presence of a direct bilirubin reaction in the blood of newborns is contrary to the observations of previous investigators. This is undoubtedly attributable to the method employed, for, as

has been pointed out earlier, similar findings on the presence of a certain amount of direct bilirubin in the blood of normal adults were observed by Malloy and Evelyn. It is apparent from the above data that while there is a marked difference in the quantity of total bilirubin for each day studied and that these amounts are to a certain degree proportional to the presence of clinical jaundice, there is an almost constant amount of direct bilirubin at all times. As a matter of fact, this quantity is much more constant than a glance at the dispersion figures indicates. A survey of the individual cases shows that by far the majority of the infants maintain a value of about 0.5 mg. % during the entire period. In the occasional cases where higher or lower values were recorded, these levels likewise tend to be maintained. It is noteworthy that this constant figure for direct bilirubin in the newborn is distinctly higher than that met with in the normal adult using the same technique. The changes in hyperbilirubinemia are therefore due to variations in the amount of the indirect bilirubin. The findings would all seem to suggest the view that the amount of total bilirubin which has been transformed so as to give the direct reaction is dependent upon the presence in the blood of some substance which is comparatively constant and relatively higher in the newborn infant.

TABLE 2.—COMPARISON OF TOTAL AND DIRECT BLOOD BILIRUBIN, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY AVERAGES BETWEEN ALL CASES DURING THE PERIOD STUDIED. (Number of Cases Averaged Per Day Are Indicated in Parentheses.)

Day.	Total bilirubin, mg. %.	Direct bilirubin, mg. %.	Hemoglobin, gm./100 cc.	Vol. of packed red cells, %.	Index of fragility.
Cord blood . . .	1.35 (53)	0.51 (51)	15.36 (52)	51.3 (51)	400 (52)
2d day . . .	3.17 (48)	0.51 (48)	15.49 (45)	49.5 (45)	346 (45)
4th day . . .	5.27 (47)	0.46 (47)	15.46 (46)	48.7 (46)	328 (46)
6th day . . .	4.21 (41)	0.51 (41)	14.93 (39)	46.8 (39)	337 (39)
9th day . . .	3.10 (41)	0.51 (41)	14.70 (39)	45.9 (39)	356 (37)

*Relation of Total and Direct Bilirubin to Hemoglobin, Volume of Packed Red Cells and Fragility of the Erythrocytes.* In Table 2, a comparative study is presented between the average values for direct and total bilirubin, and the findings on hemoglobin, volume of packed red cells, and fragility of the erythrocytes previously reported by us in Part I of this study.<sup>31</sup> It will be observed at once that the total bilirubin values rise to the fourth day after which they fall, while there is a steady decrease after the second day in the averages for hemoglobin and volume of packed red cells. Further, the total bilirubin is highest at the time when the resistance of the red cells, as determined by the fragility index, is greatest. Similar

observations were made on the infants with and without jaundice (see Table 1).

It is apparent, therefore, from the above that hyperbilirubinemia decreases steadily after the fourth day in spite of the fact that there is a continued blood destruction as evidenced by the fall in hemoglobin and volume of packed red cells. It is interesting to observe that as the bilirubin concentration rises, the hemolytic index falls (increased resistance) and conversely, that as the bilirubin falls the index rises. While this might suggest that a change in resistance of the red cells is dependent upon the degree of bilirubinemia, a day-to-day comparison of the variations in the index with the degree of hyperbilirubinemia between icteric and non-icteric infants makes it obvious that no such relation exists. Thus we found on the second-day venous bloods of icteric infants that there was a greater increased resistance and a greater bilirubinemia, while on and after the fourth day the icteric group showed a lessened increased resistance though a still greater bilirubinemia than did the non-icteric infants.

*Relation of Hyperbilirubinemia to Blood Destruction.* In order to study in detail the relationship between blood destruction and the degree of hyperbilirubinemia, we calculated the fall in hemoglobin for each individual infant during the 9-day study and plotted it against the maximum bilirubin concentration for that infant. Chart 1 indicates that we were unable to demonstrate any relationship between the extent of hemoglobin reduction and the rise in bilirubin. The chart further shows there is no difference in this respect between the icteric and non-icteric infants. A similar chart, not reproduced here, giving the reduction in volume of packed red cells instead of hemoglobin, likewise failed to indicate any direct relationship between the amount of blood destruction and bilirubinemia.

We then constructed scatter charts for each day studied in which the changes in hemoglobin and volume of packed red cells were compared with the amount of total bilirubin on that day. Of these charts, which present an essentially similar picture, that for hemoglobin on the fourth day (Chart 2) only is reproduced here, and it will be found that no relationship exists between the fall in hemoglobin which has occurred since the cord blood determination and the increase in blood bilirubin over the same period.

Furthermore, an attempt was made to demonstrate, if possible, any relationship between the original height of the hemoglobin and the bilirubinemia. For this purpose, the 10 infants having the highest cord blood hemoglobins were compared with the 10 infants with the lowest values. The average fall in hemoglobin in 9 days for the first groups was 1.4 gm., while the average fall for the second group was 0.16 gm. Notwithstanding the marked difference in amount of blood destruction indicated between the two groups, the



average maximum bilirubin of the group with the high initial hemoglobin was 4.59 mg.%, while the average maximum bilirubin for the groups with the low initial hemoglobin was 4.08 mg.%. As will be appreciated, this is a negligible difference and again indicates no relationship between the amount of blood destruction and the degree of bilirubinemia present. A similar finding was obtained using volume of packed red cells instead of hemoglobin.

Hemoglobin,  
gm./100 cc.

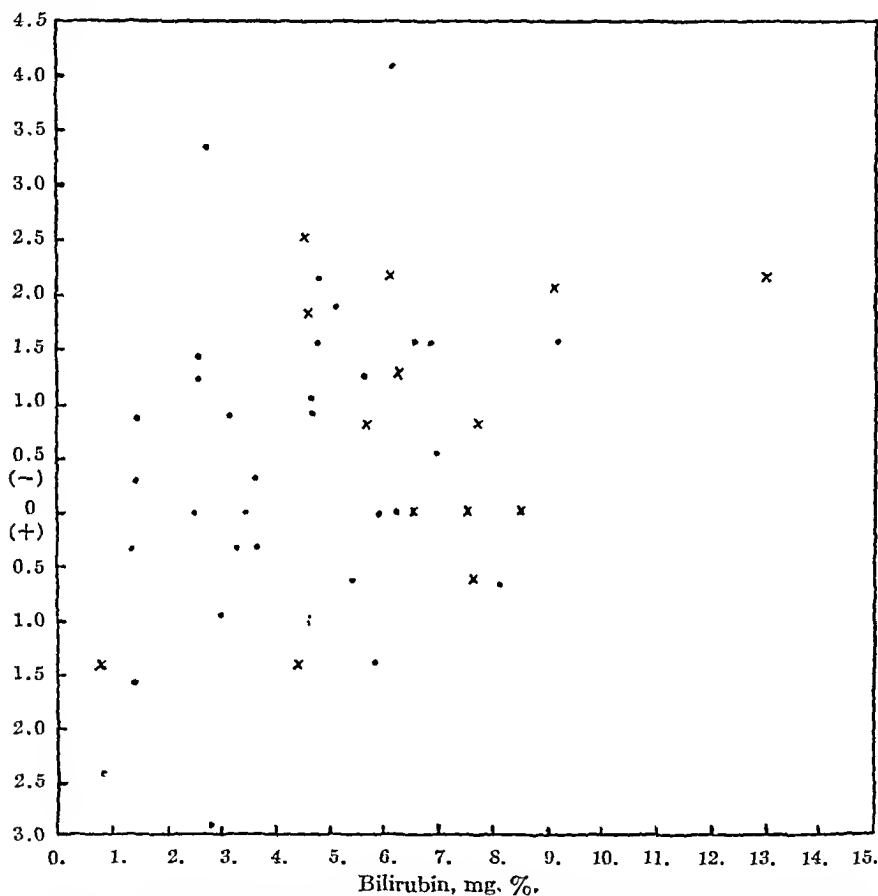
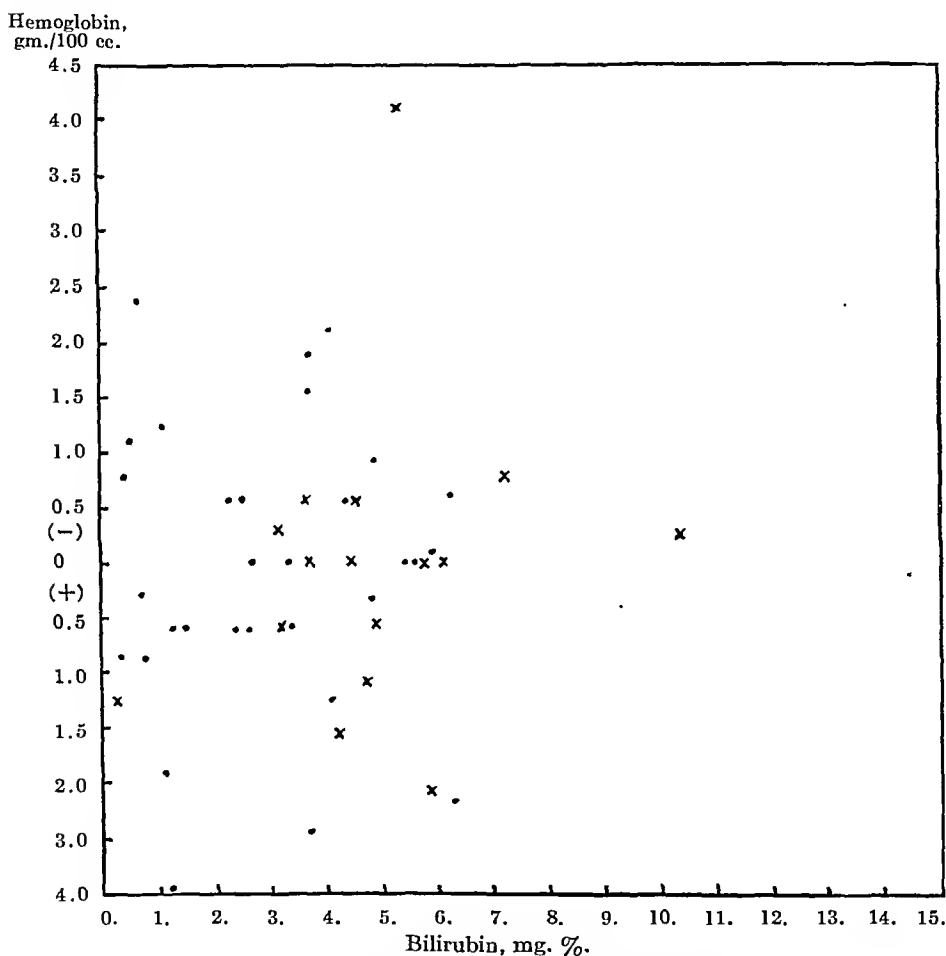


CHART 1.—Relationship between the total individual changes in hemoglobin at the end of the 9 days and the greatest total bilirubin concentration during this period. In this and subsequent charts, icteric infants are indicated with a cross; non-icteric with a dot.

Having failed to demonstrate any relationship between the reduction of hemoglobin and volume of packed red cells and the hyperbilirubinemia, we then took up the question of the hemolytic index for fragility of the red cells to demonstrate whether there was any indication that an infant having a high index of fragility showed a greater bilirubinemia. We plotted in a scatter chart the total

bilirubin on the day it was greatest against the index of hemolysis at that time. This is shown in Chart 3, and it will be observed that no relationship was found to exist either for the icteric or non-icteric infants or the group as a whole.

During the course of our study on normal infants, determinations on several cases of erythroblastosis were carried out. The series is, of course, too small for definite conclusions but the findings are



It is noteworthy in contrast to the normal infants that children with erythroblastosis are born with a higher total bilirubin but similar direct bilirubinemia. This is in agreement with the clinical evidence that jaundice in these cases is often noted at birth. The total bilirubin then rises rapidly to a much higher figure than met with in the icteric group of normal infants. Moreover, by the third day, the direct bilirubin shows a distinct rise in contrast to the

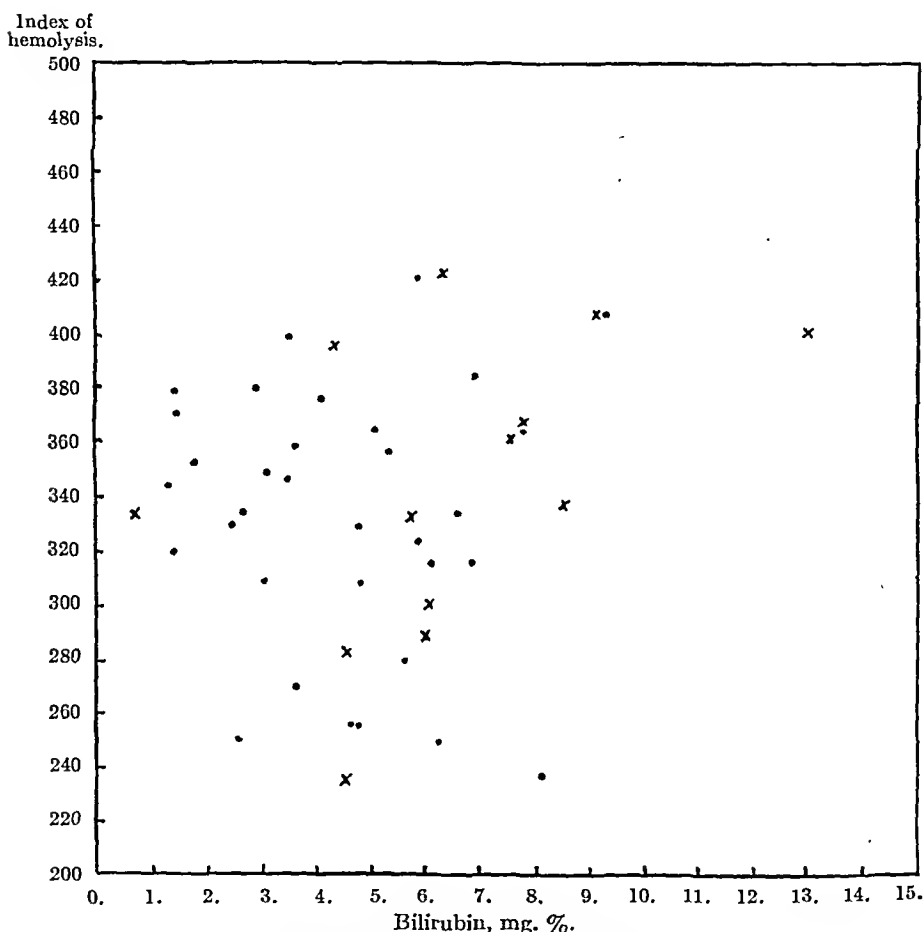


CHART 3.—Relationship between the highest individual total bilirubin observed and the index of hemolysis at that time.

constant figures for the normal infants. This is possibly referable to biliary thrombi often reported in these cases.<sup>26</sup> In Part I of this study we noted in erythroblastosis a distinctly high hemolytic index (increased fragility) for the red cells, and a marked progressive anemia. These infants alone of all those studied showed an increased fragility. There is, therefore, every indication that in this condition we are dealing with a hemolytic form of anemia and by no

means, as some have suggested, simply with an icterus neonatorum of unusually severe degree.

**Summary.** Our results on 250 bilirubin determinations on newborn infants during the first 9 days of life demonstrate a state of hyperbilirubinemia at birth which increases during the first 4 days, then falls toward normal. Thirty per cent of our cases developed icterus neonatorum. When we compared the presence of clinical icterus with the degree of hyperbilirubinemia, it was found that in a general way icterus was reported when the level of total bilirubin reached 5 mg. % or more. There were cases, however, where icterus was reported with lower blood values, as well as cases where icterus was apparently absent with figures above this level. It would appear all newborn infants are reacting similarly to the readjustments of postnatal life whether they develop clinical jaundice or not.

We have attempted with the material at our disposal to determine the existence of any relationship between the amount of blood destruction taking place during the first few days of life and the degree of hyperbilirubinemia and the development of icterus neonatorum. For this purpose we have shown: (1) that there is a continuous fall in hemoglobin and volume of packed red cells throughout the period studied, while the bilirubinemia reaches its greatest level on or about the fourth day and then declines toward normal; (2) that no relationship exists either between the individual total fall in hemoglobin and volume of packed red cells and the amount of bilirubinemia during the 9 days studied or between the changes in hemoglobin and volume of packed red cells and the total bilirubin concentration on any particular day; (3) that there is no relationship between the original height of the hemoglobin and the volume of packed red cells, and the development of hyperbilirubinemia. Further, as was noted in Part I of this study, no correlation could be demonstrated between the original height or subsequent changes in the individual values for hemoglobin and packed red cells and the appearance of clinical jaundice. (4) We have clearly shown the resistance of the erythrocytes to be increased during the period studied, and that variations in the index of hemolysis in normal infants have no effect upon the degree of hyperbilirubinemia which develops. (5) In our various studies on the relationship of blood destruction and fragility of the erythrocytes to the degree of bilirubinemia, no significant differences could be found to exist between the icteric and the non-icteric infants. These findings all refute the conclusions of those who have supported the hypothesis that the development of icterus neonatorum is dependent upon the amount of blood destruction or the presence of an abnormal hemolytic condition in the blood at the time of birth. It is, of course, quite apparent that the presence of an increased blood destruction allows for the production of a large amount of bilirubin in a comparatively short time and makes possible the development of an

excessive amount of blood bilirubin. However, neither the height of the bilirubinemia nor the consequent development of icterus neonatorum bears any direct relation to the amount of blood destruction in the individual case.

There is nothing in our findings which contradicts the views of those who explain the development of jaundice on the basis of variations in the ability of the liver cells to excrete the excessive bilirubin transported to them at this time. While our observations do not prove the hepatogenic theory, their lack of any contradiction offers strong support for it, especially when taken into consideration with the literature briefly reviewed earlier. We are, therefore, of the view that hyperbilirubinemia in general and icterus neonatorum in particular are made possible by the increased blood destruction which is obviously taking place during the first few days of life, but, that whether the infant develops a sufficient bilirubinemia to exhibit clinical icterus is dependent upon the functional ability of the liver cells to excrete it.

The methods employed have allowed for a quantitative analysis of the amount of bilirubin giving the direct and indirect reactions. It has been demonstrated that the hyperbilirubinemia in the normal infant during this period, whether it reaches a level sufficient to produce icterus or not, is due entirely to a rise in the indirect bilirubin, while the direct bilirubin maintains an extraordinarily constant level.

In the few cases of hemolytic anemia of the newborn (erythroblastosis) which came under our observation, it was demonstrated that these infants are born with a hyperbilirubinemia which reaches a much higher figure than in the normal infant, whether jaundiced or not. Moreover, while the direct bilirubin was not increased as compared with the normal infant at birth, it likewise tended later to rise, suggesting the development in these cases of an associated obstructive factor. At the same time it was observed that these cases showed an increased fragility of the red cells and a severe anemia as compared with the normal infants. This we believe is indicative of a different process from that which is taking place in icterus neonatorum.

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## THE DOUBLE QUOTIDIAN TEMPERATURE CURVE OF GONOCOCCAL ENDOCARDITIS. A DIAGNOSTIC AID.

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IN his monograph on septicemia, Lenhartz<sup>7a</sup> described the usually constantly elevated, weakly remitting temperature curves of staphylococcal and pneumococcal bacteremia, the irregularly intermittent curves of streptococcal and colon bacillus bacteremias, and the somewhat similar, high, intermittent fever accompanied by frequent shaking chills seen in gonococcal sepsis. Other authors have been struck by the highly regular, often quotidian variations in the fever of gonococcemia,<sup>3,8</sup> and the temperature curves seen in gonococcal endocarditis have been subdivided into those: *a*, continuous with remissions; *b*, essentially intermittent; and, *c*, intermittent and remittent.<sup>10,12</sup> While it is thus general knowledge that, as a rule, in gonococcal endocarditis the oscillations in the fever through the 24 hours are greater and at the same time often more uniform from day to day than in other forms of bacterial endocarditis, there is no general recognition of one particular form of temperature curve which would seem relatively specific for gonococcal endocarditis. This special temperature curve is the subject of this paper.

Horder,<sup>3</sup> in 1909, writing on general aspects of bacterial endocarditis, presented temperature charts of 2 patients stated to have gonococcal endocarditis; each chart showed *two* peaks of temperature each day, one in the morning and one in the evening, for a period of several days, with a rapid fall to normal or subnormal levels following each peak. He also referred to a somewhat similar chart of a case reported by other authors<sup>2</sup> and stated that double

quotidian intermittent fever was common in gonococcal endocarditis. More recently, Horder and Gow<sup>4</sup> commented that the appearance of 2 spikes in 24 hours on a temperature chart suggests gonococcal septicemia or kala-azar. Lenhartz,<sup>7b</sup> even earlier than Horder, described a patient with probable gonococcal endocarditis and presented a temperature chart which he characterized as "intermittens quotidiana duplicata." Other authors writing on gonococcal endocarditis have described similar temperature curves in individual cases, either without any significant comment whatever in the text,<sup>5,6,11</sup> or, like Lenhartz, with merely a note on the peculiarity of the curve in the particular case (Harris and Johnston,<sup>2</sup> Oettinger, Marie and Morancé,<sup>9</sup> and Thayer<sup>12</sup>). The only writer other than Horder and Gow to note that this temperature curve is character-

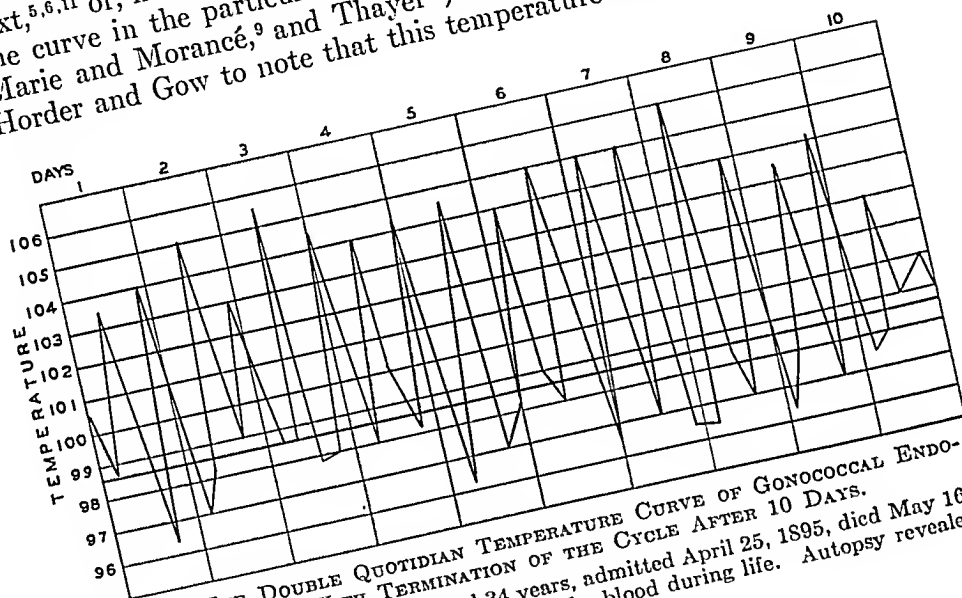


FIG. 1.—THE DOUBLE QUOTIDIAN TEMPERATURE CURVE OF GONOCOCCAL ENDO-CARDITIS WITH TERMINATION OF THE CYCLE AFTER 10 DAYS.  
L.S., M4891, a white female aged 34 years, admitted April 25, 1895, died May 16, 1895. The gonococcus was cultured from the blood during life. Autopsy revealed that the endocarditis involved the mitral valve.

istic of gonococcal endocarditis was R. H. Williams,<sup>13</sup> who, in commenting on the great frequency of chills in this disease, emphasized that almost daily "double peaks" occurred on the temperature charts of 6 of his 12 patients. It was during our association with Dr. Williams in 1938 that, when the diagnosis was still in doubt, he pointed out the significance of the double peaks on the chart of a patient with a cardiac murmur subsequently demonstrated to have gonococcal septicemia (reported elsewhere<sup>1</sup>); thereby he stimulated us to determine the incidence of the phenomenon in the patients with gonococcal endocarditis observed at the Johns Hopkins Hospital.

The temperature charts of 24 patients with gonococcal endocarditis were examined. The diagnosis was established by post-mortem examination in 22. Of these autopsied cases in, 12 blood

cultures made during life were positive for the gonococcus; in 2 others there were positive cultures from the endocardial vegetation after death; and in the remaining 8 cases, Gram-negative diplococci were found in the smears made from the vegetations, though they could not be cultivated. Of the 2 cases not autopsied, 1 had a blood culture positive for the gonococcus before death, postmortem examination being refused; another patient, whose blood culture was also positive, recovered from her illness.<sup>1</sup> All of these 24 patients were in the hospital for 6 days or longer; we did not examine the records of several other patients who were on the wards for only 1 to 3 days, since the temperature charts on these patients were too brief to be evaluated.

Ten of the 24 charts showed the double peaks for a period of from 5 to 22 consecutive days, averaging 10 days. An eleventh chart had shown the double peaks for one day when, on the second day following admission, the patient was treated with sulphanilamide with a consequent modification of the temperature curve. Thus 11 of the 24 patients (46%) showed the double peaks.

The prototype of these 11 patients is one who, at 6 A.M., has a shaking chill lasting a few minutes followed by a rise in rectal temperature from an initial level at 4 A.M. of 98° to 105° at 8 A.M., with subsequent sweating and a precipitous fall to 98° at 4 P.M. Then follows repetition of the chill and the rest of the episode at 6 P.M., and the temperature returns to 98° by 4 A.M. of the next day only to renew the 12-hour cycle. There was moderate variation in the timing of the episodes from day to day in the same patient. Thus the chill may come at 8 o'clock instead of 6 o'clock; 1 patient temporarily had peaks at noon and midnight, the fever subsequently returning to the more common morning and late afternoon elevations. For a period of several days the interval occupied by the cycles may be 10 or even 8 hours, with two and a half to three cycles a day. It is very common for an occasional cycle in the series to be abortive, or for one cycle to last longer than the usual 12 hours, so that there may be only one peak during the course of 24 hours, with reversion to the 12-hour cycle the next day. Thus in our series of 11 cases a total of 184 peaks were observed in 103 days. The chills also may vary markedly in intensity from day to day. Usually the fever is intermittent, falling below 98.6°, and not infrequently to 97° or 96°, after the fastigium. In 1 patient, however, the fever was constantly sustained, with the superimposed double quotidian variation producing a regularly remittent character. These cycles we describe are not due to the administration of antipyretics, which were withheld in most of the cases. They were best demonstrated by taking the patient's temperature every 2 hours. Some patients were prostrated by their disease; others suffered it with a remarkable temporary appearance of well-being.

It should be emphasized that the charts described did not show



the double-peaked temperature curve during the whole period that the patient was observed, or even during the majority of it. Usually a patient with a previously intermittent curve lapsed temporarily into the 12-hour cycles for a period of 1 to 3 weeks, the curve subsequently becoming irregular again. Only 2 moribund patients ran the cycle with any regularity; a tendency to flattening and lowering of the temperature curve terminally in endocarditis has already been commented on by Horder<sup>3</sup> and Thayer.<sup>12</sup> The cycles were commonly present at any time from early in the disease until the last week. On more than one occasion a patient at the time of admission related that he had been subject to 2 chills daily since his symptoms had begun. All of the 4 patients with gonococcal endocarditis which have been treated with sulphanilamide at this hospital were running the double quotidian fever when the drug was first administered; the double peak disappeared within 48 hours, and there was subsequent lowering of the temperature curve in all of them. The phenomenon therefore will probably not be observed in patients receiving sulphanilamide.

The occurrence of the usual 12-hour cycles could not be correlated with any particular valve involved by the gonococcal vegetation; the pulmonic, mitral or aortic valves were involved in our 11 patients with no significantly predominant site. There was no correlation with the duration of the course of the disease or with the stage of the illness at which the patient was observed, save that, as already noted, the cycles were uncommon in the last week of life.

In the patients who never showed the cycles, or in those who were not showing them for the time being, the fever was usually high and intermittent, often with a regular 24-hour cycle and diurnal variations from 5° to 7°; slightly less commonly the fever was remittent, and frequently the curve was intermittent at one period of the disease and remittent at another.

The charts of 3 patients with gonococcal septicemia uncomplicated by endocarditis were examined. None of the 3 showed sustained double peaks, although 2 of them showed an irregular, double quotidian curve for 48 hours.

A small series of 13 charts of patients who had been demonstrated at autopsy to have an endocarditis due to the beta hemolytic streptococcus was examined; the patients had died before the advent of sulphanilamide and hence their course was uninfluenced by that drug. It was thought that, since hemolytic streptococcal septicemia often produced high, intermittent fever, the double peak phenomenon might also be present in that type of endocarditis. Two of the 13 charts did show a suggestion of double quotidian fever, but in these 2 cases the curve was remittent rather than intermittent, the swings were of only 1° or 2°, and the cycle was never consecutively repeated for more than 48 hours. Thus neither

these charts, nor those of streptococcal septicemia presented by Lenhartz,<sup>7a</sup> were really similar to those of gonococcal endocarditis which we have described above. Recently there came to autopsy 2 patients who for 3 and 7 days respectively ran remittent fevers with irregular double peaks. One patient had an anaërobic gamma hemolytic streptococcal septicemia secondary to an infected abortion, and the other a pyelephlebitis due to a staphylococcus and an unidentified Gram-negative bacillus.

The explanation for the 12-hour febrile cycle in gonococcal endocarditis is not apparent to us. We merely emphasize the phenomenon as a valuable aid to diagnosis in those cases in which it occurs, feeling that it deserves somewhat more prominence than is assigned to it in the papers already cited.

**Summary.** A study of the temperature charts of 24 patients suffering from gonococcal endocarditis showed that in 11 there was a striking double quotidian variation in fever lasting over a period of from 5 to 22 days.

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## RÔLE OF THE "STATIC BLOOD PRESSURE" IN ABNORMAL INCREMENTS OF VENOUS PRESSURE, ESPECIALLY IN HEART FAILURE.

### I. THEORETICAL STUDIES ON AN IMPROVED CIRCULATION SCHEMA WHOSE PUMPS OBEY STARLING'S LAW OF THE HEART.

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GENERALIZED congestion of the veins has always been a symptom on which clinicians have laid much stress. Occurring so often late in the course of chronic cardiac disease, it has generally been inter-

preted as indicating incompetence of the heart muscle. The idea that "back pressure" caused venous congestion when the heart weakened followed the recognition of mitral stenosis. The analogy between venous congestion and the effect of a dam on a stream of water was put forward at that time.<sup>8</sup>

The experimental era dates from Cohnheim,<sup>2</sup> who injected fluid into the pericardium of dogs to handicap the heart. In these experiments the venous pressure rose and so this venous congestion was attributed to cardiac weakness. However, the arterial pressure fell in Cohnheim's experiment; that this did not occur in clinical congestive heart failure was unknown to this author for it was not discovered until 1905. Therefore these experiments did not produce a condition analogous to clinical congestive heart failure, as was then believed. Analogies between clinical congestive failure and the behavior of a simple circulation schema were emphasized by Starling as early as 1897.<sup>13a</sup>

Because of these and many other observations a view of the mechanism of congestive failure was evolved which was so widely accepted by clinicians that we shall call it the classic view.<sup>13a</sup> It may be summarized as follows. The primary cause is believed to be weakness of the heart muscle. Compensated for a time by hypertrophy and dilatation, eventually increasing weakness results in a diminished cardiac output which initiates two trains of events. First, as a metabolic consequence of the slow circulation, the oxygen supply to the body's tissues is reduced, their normal metabolism is interfered with, and a characteristic train of symptoms results. Second, as a *mechanical* consequence of the diminished circulation, blood accumulates in the veins, produces passive congestion of organs, raises the venous pressure, and so leads to another familiar train of symptoms. This view was generally accepted before measurement of cardiac output was possible.

The results of estimations of cardiac output in congestive failure have led some authors to question the correctness of the classic viewpoint.<sup>7</sup> All agree that the average cardiac output found in congestive failure is smaller than the average found in normal persons. But when the results obtained in individual cases are considered there is evidence that many cases of congestive failure have a higher cardiac output than many persons without this complication, that the severity of the symptoms has no invariable relation to the output, and that improvement is not always accompanied by increase in output. So certain authors believe that reduced cardiac output is no essential part of congestive heart failure.<sup>7</sup>

In the face of these facts several courses are open to students of the subject. The classic view may still be supported.<sup>4,7</sup> The averages of all the cardiac output results, and the results obtained in some patients, are consistent with this view. The discordant results are only found in some individuals and, as cardiac output methods

are not highly accurate, chance accumulation of errors would account for some of the discrepancies.<sup>9</sup> Although the most careful experimenters have employed special precautions to safeguard their results, the extra difficulties inherent in estimating cardiac output when the lungs are congested are generally recognized. We are aware of a number of investigators who, after attempting to estimate cardiac output in congestive failure, decided that it could not be done with enough accuracy to make the effort worth while.

Other authors, accepting the cardiac output results as inconsistent with the classic view, have modified their ideas of the mechanism of congestive failure. Thus Altschule<sup>1</sup> points out that the cases of congestive failure with normal cardiac outputs have abnormally high metabolic rates. He believes that congestive failure occurs because the supply of oxygen and other metabolites is insufficient to meet the tissue demand, not because cardiac output diminishes below a certain level. This concept reconciles the cardiac output results with one part of the classic viewpoint, but it throws no light on the mechanism of the venous congestion in this condition. According to Harrison's view,<sup>7</sup> venous congestion with a normal cardiac output may be attributed to a weakness of one side of the heart relative to the other, the blood accumulating before the weaker heart. McMichael<sup>10</sup> thinks of the congestive phenomena as being a mechanism by which the body compensates for cardiac weakness, not as a mechanical consequence of a diminished circulation.

Our interest began with the discovery that certain patients with small hearts had abnormally small cardiac outputs relative to the size of their bodies.<sup>16</sup> According to the classic view one would have expected venous congestion. But none was present, and in the 5 years that have elapsed none has developed in the cases followed. This observation indicated clearly that venous congestion was no necessary mechanical consequence of a diminished circulation, and led to a decision to investigate the other factors which might bring it about.

Reviewing the literature we found the view that venous congestion was directly caused by cardiac weakness to be supported by mechanical analogies of a very crude sort, like the effect of a dam on a flowing stream and the behavior of circulation schemata with mechanical pumps which, unlike the heart, sucked fluid from the "veins." The failure to reproduce this feature prevented any adequate simulation of the double mammalian circulation with two pumps.

Our plan was to construct a circulation schema which behaved in a more physiological manner than its many predecessors; and, having ascertained the causes of venous congestion when one or both sides of its "heart" were weakened, to undertake a similar analysis in the clinic which, we hoped, might throw light on some of the per-

plexing problems of "congestive heart failure." Preliminary reports on this work have already been published.<sup>14,15</sup>

Accordingly we constructed a two circuit schema whose pumps obeyed Starling's "Law of the Heart," and its behavior made us see the problems of venous congestion in a new light. This experience forms the subject of this paper. In a second paper the clinical research, suggested by the behavior of our schema, is recorded.

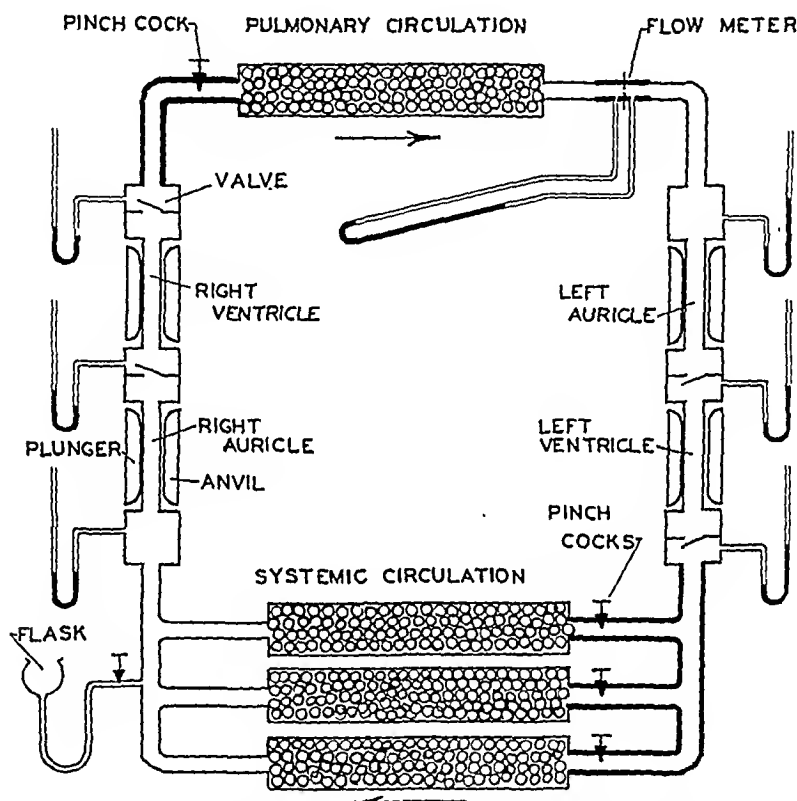


FIG. 1.—GENERAL ARRANGEMENT OF SCHEMA. Arterial portions, made from thick walled rubber pressure tubing, are shown by heavy lines. Venous portions, made from very flexible drainage tubing, are shown by light lines. Capillary beds are made from large Gough tubing, filled with glass beads. Manometers are connected through short lengths of glass capillary (not shown) to damp oscillations. The flow meter is a thin plate inserted in a short length of metal tube. The diameter of the orifice in the plate is approximately one-half the inside diameter of the tube. Pressure taps immediately above and below the plate lead to a sloping tube manometer.

**Apparatus.** The schema has about one-tenth the "blood volume" and "cardiac output" of a normal man. The "heart" rate can be varied from 50 to 150 per minute.

The plan and details of construction can be seen from Figures 1 and 2. The cams were designed from data in Wiggers' book,<sup>19</sup> and, although the cam follower did not always follow the cam at high speeds, optical records showed that the arterial pressure curves approximated those obtained in experiments on animals.

Excursion of the mercury manometers was damped by the use of short lengths of 1 mm. bore glass tubing, as only mean pressures concerned us.

At first, in order to mimic blood viscosity, the system was filled with 30% sugar solution (sp. gr. = 1.127). In the later experiments, water was used without any noteworthy change in results.

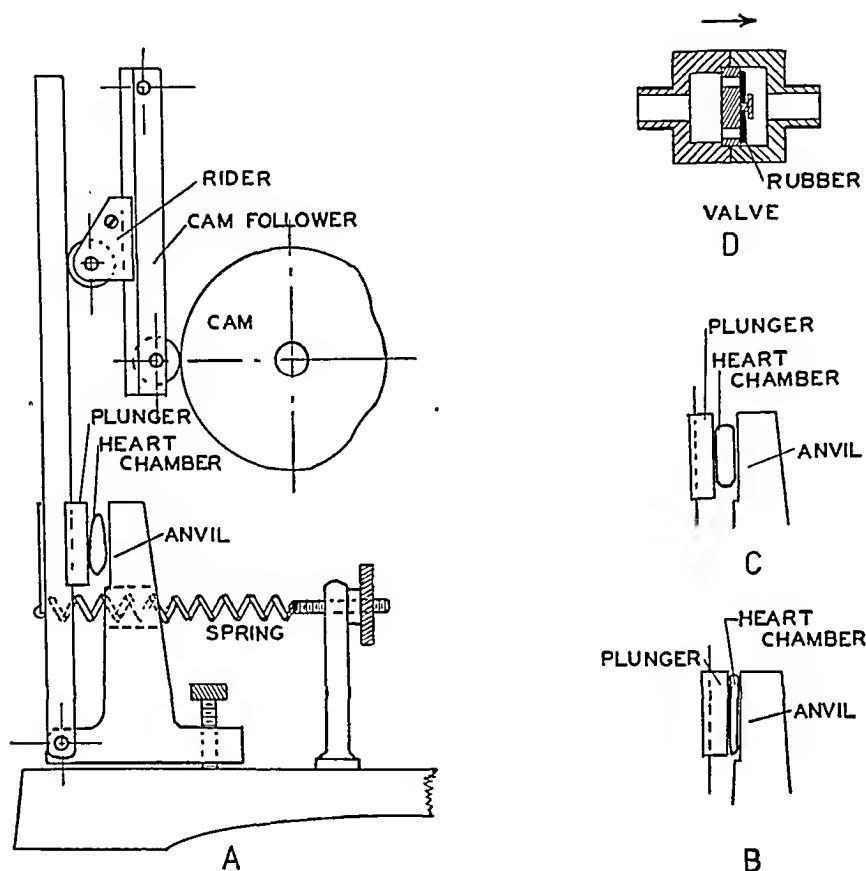


FIG. 2.—MECHANICAL ARRANGEMENT OF HEART CHAMBERS. A  $\frac{1}{2}$  H. P. shunt motor (Janette Mfg. Co., Chicago, Ill., Type 1-DS-16) with two built-in 16 to 1 reduction gears, drives four cams, one for each chamber. The motor speed is controlled by field and armature rheostats.

A. Heart chamber is contracted by spring pulling plunger towards anvil. Heart chamber is relaxed by cam acting through cam follower and rider. Moving rider along cam follower varies length of stroke of plunger. Heart chamber is shown relaxed and only partly filled, as occurs with low venous pressure.

B. Heart chamber contracted.

C. Heart chamber relaxed and completely filled as occurs with high venous pressure.

D. Detail of valve. Soft rubber disk seats against perforated metal disk.

The flow meter was calibrated by opening the system and allowing the pumps to pump from a reservoir into a container. The differential manometer could be read to 1 mm., the arms having a difference of 4 cm. at the highest flows used. At low flows a considerable error was involved, some of the points obtained deviating from the ideal calibration curve by 10%.

"Heart" work has been approximated by the formula: work = flow  $\times$  pressure, the figure employed for pressure being the difference between the mean pressures of the damped arterial and venous manometers. Thus the

velocity factor and the component of work utilized within the heart were not estimated.

Resistances were calculated from the formula  $R = \frac{\text{Pressure drop}}{\text{Flow}}$ .

Before each experiment the resistances were adjusted to give physiological pressures throughout the system and the ventricular springs were set so that the work of the right "heart" equaled about one-third that of the left.

**Experimental. *The Properties of the Schema.*** Starling's experiments<sup>11</sup> involving the measurement of the heart's work and volume could not be duplicated on our schema due to difficulties in measurement of the "heart's" volume. Therefore we contented ourselves with measuring the relation between "venous" filling pressure and the "heart's" work. It seems obvious that the "heart's" volume would be dependent on filling pressure at any constant heart rate. Figure 3 shows the results.

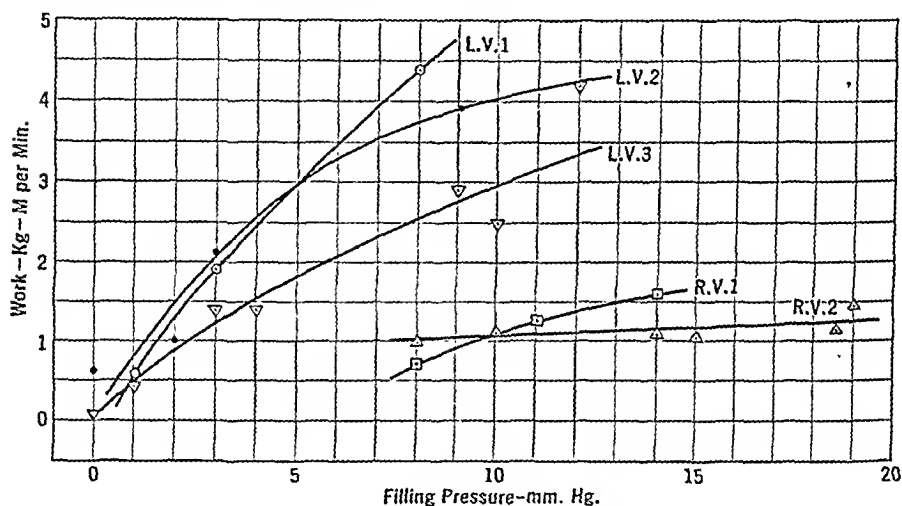


FIG. 3.—Curves illustrating the relationships between filling pressure and work in the pumps of our schema. In R.V.2 cardiac failure has been simulated by weakening the spring. The other curves show the response to increased filling when strength is intact.

The simulation of Starling's "Law of the Heart"<sup>13b</sup> is brought about by the schema as follows: As the "heart" fills, the band tubing changes its shape; flattened when empty, it becomes more cylindrical as it is filled. During "systole" the spring's force is exerted partly on the fluid and partly against the cam. The fuller the "heart," the greater is the proportion of the spring's force expended on driving the fluid, and the less the proportion lost in pressing against the cam. So increased filling leads to a greater output of work by the pump.

If the spring is weakened beyond a certain point, all its power is applied to the fluid and none to the cam. Under these conditions increased filling no longer causes increased work, an analogy to what is found in physiologic heart failure.<sup>11</sup> Curve R.V.2 (Fig. 3) illustrated this point.

*The Definition and Measurement of Static Blood Pressures.* Our studies emphasize the great importance of the pressure existing throughout the "vascular" system when the pumps are stopped. This static pressure is named the *mean systemic pressure* in Starling's textbook.<sup>13c</sup> The term is introduced in a discussion of a simple schema with a single pump. Applied to our schema, or to the mammalian circulation, the term chosen by Starling is confusing as it suggests the mean of the arterial, capillary, and venous pressures in the systemic circulation during heart action. Therefore we propose to avoid a term so likely to be misunderstood and to call this property of any fluid system, the pressure which persists throughout the entire circulation after cardiac action has stopped, the *general static pressure*.\*

TABLE 1.—THE EFFECT OF WEAKENING ONE OR BOTH SIDES OF THE SCHEMA'S "HEART."

Exp. No.	Static pressures measured with circulation stopped.			Pressures measured during circulation.				Cardiac output (cc/min.)	Heart work.		Heart rate (per min.).	Remarks.
	All vessels open.	Great veins clamped.		Systemic		Pulmon-ary.	Left (gm. meters per min.).		Right (gm. meters per min.).			
		General static pressure (mm. Hg.).	Systemic pressure (mm. Hg.).	Pulmonary pressure (mm. Hg.).	Arterial (mm. Hg.).	Venous (mm. Hg.).				Arterial (mm. Hg.).		
1A	13	11	15	95	5	26	8	172	203	49	90	Initial readings Both hearts weakened Systemic resistance in- creased by tightening screw clamps Clamps as in A and B. Fluid added to circula- tion
B	13	12	16	65	8	21	9	120	92	21	90	
C	13	12	16	95	6	24	12	87	98	21	90	
D	34	31	40	93	27	49	34	172	138	51	90	
2A	13	13	18	90	7	30	13	198	152	46	72	Initial readings Right ventricle out Fluid added
B	13	14	10	65	12	14	6	122	98	3	72	
C	27	30	22	105	27	27	14	158	196	..	72	
3A	13	12	20	79	8	32	10	174	163	57	90	Initial readings Left ventricle weakened
B	13	11	21	45	5	35	19	100	35	41	90	

The general static pressure was always measured with the "heart" stopped in both "systole" and "diastole"; the figures given in Table 1 are the averages of the values obtained. Care was always necessary to ascertain whether any manipulation of the schema, such as weakening a "heart" or changing a resistance, altered the static pressures.

\* In a preliminary report we called this pressure the "non-cardiac pressure." We later found that the term "static pressure" had been employed previously by Bolton. The use of the older term seems preferable to the introduction of a new one.



If such alteration was found it was corrected by adding or withdrawing small amounts of fluid from the system.

In some experiments we studied the volume of fluid and the static pressures in both the "systemic" and "pulmonary" circuits. With the circulation flowing, hemostats were placed simultaneously on both great "veins," and then the pumps were stopped immediately. This maneuver was repeated at least four times to guard against occasional failure to obstruct the "veins" simultaneously. After equilibrium within each circuit had occurred, pressures were measured with the "hearts" stationary in both systole and diastole, the averages giving the "pulmonary" and the "systemic" static pressures respectively.

**Results and Discussion.** The results of certain important experiments have been recorded in Tables 1 and 2.

*Effect of Weakening One Side of the Heart.* As soon as one "heart" is substantially weakened the other "heart" is not filled so full and accordingly, although its strength is intact, the work it performs on the circulation is reduced. The magnitude of this effect depends on the general static blood pressure. Thus, if this pressure is low, weakening the right "heart" has a far greater effect on the left "heart's" work than if this pressure is high (Table 2).

TABLE 2.—EFFECT OF COMPLETE FAILURE OF "RIGHT VENTRICLE" AT DIFFERENT LEVELS OF GENERAL STATIC BLOOD PRESSURE.

(Ratio of "right heart" to "left heart" work before failure = 1:2.3 in each exp.)

General static blood pressure (mm. Hg).	"Cardiac output" after failure of R. V. in % of its value while R. V. was normal.	Left "heart" work after failure of R. V. in % of its value when R. V. was normal.
7	42.5	22
13	55	65
21	60	68

*Increased Static Blood Pressure as a Means of Compensation for Heart Failure.* If fluid is added to the circulation, the static pressure is increased, and cardiac output and work increase also. In this respect the schema behaves like the closed circuit heart-lung preparation of Daly.<sup>3</sup> In the same manner increased static pressure can partly or completely compensate for weakness of one or both sides of the "heart." Table 1 gives typical examples of these effects. But it should be pointed out that while the diminution of flow resulting from complete failure of the weaker right "heart" can be restored by an increased static pressure, only partial failure of the stronger left "heart" can be compensated by this means.

*Hydraulic Principles Concerned in Failure of the Circulation.* The behavior of a simple schema with tubes of uniform elasticity and a single pump is well described by Starling.<sup>13a,c</sup> With the pump at rest the general static pressure read from a manometer open to the air, indicates the terms of equilibrium with the environment. Start the pump, the internal pressure at one point remains at the

static pressure, fluid accumulates on the arterial and diminishes on the venous side of this point; and the pressure on the "arterial" side becomes higher, on the "venous" side lower than the static pressure. Slow the circulation and both "arterial" and "venous" pressures approach the static pressure as fluid leaves the arteries and accumulates in the veins. Thus weakening the heart causes an increase of "venous" pressure.

Our schema has two pumps, and two sides of the circulation, so additional factors enter into its behavior. When the left "heart" is weakened, without altering the clamps controlling the resistance (Table 1, Exp. 3), fluid accumulates in the "pulmonary" side and diminishes in the "systemic" side. If the circulation is now stopped by the simultaneous clamping of both great "veins" as described on page 33, the static pressure is higher in the "pulmonary" than in the "systemic" side. Therefore the behavior of our schema is controlled by the principles described by Starling for a simple schema, superimposed on its ability to shift fluid from one side to the other.

*Factors Concerned in Elevating the Venous Pressure.* With these fundamental principles in mind, the hydraulic factors which control venous pressure may be analyzed by dividing them into three groups.

Group 1 contains the factors which control the distribution of fluid between the arteries, capillaries and veins on each side.

Group 2 contains factors which control the distribution of fluid between the systemic and pulmonary circuits.

Group 3 contains the factors which change general static blood pressure and so alter pressures all around the circulation, the change appearing most conspicuously where pressures are lowest, *i. e.*, in the veins. Such an increase of venous pressure may be brought about by the introduction of fluid within the elastic vessels, by increased tension exerted by the vessel walls themselves as in widespread vasoconstriction, and by increasing the external pressure on the fluid-containing vessels as when edema stretches the skin. In our schema a given increment of static pressure causes a smaller increment of "venous" pressure. This is because the "heart" is stimulated as its filling pressure increases, the circulating is accelerated, and the factors of Group 1 antagonize those of Group 3. So the ability of the heart to respond affects the net result.

If any increase of venous pressure found in the clinic, could be analyzed to find which of these factors predominated, much insight into its etiology and significance would be gained. In the paper which follows this we have attempted such an analysis and the results are to be found therein. But in the clinical literature a rise in venous pressure is frequently explained by other analogies and two must be described in detail as our schema demonstrates certain aspects of the hydraulics which have not always been fully appreciated.

*The Dam and Stream Analogy.* Following many examples in the older literature, Wenckebach<sup>18</sup> likens the rise in venous pressure after cardiac weakness to the rise of pressure upstream from a dam constructed in a river. If one obstructs a river by building a dam, pressure upstream rises until the flow over the dam equals the inflow. The dam has no effect on the source of power upstream and so no lasting effect on the flow.

The situation in our schema after partial obstruction of the "vena cava," or after weakening the "heart," is very different. As soon as such an obstruction is established the right "heart" does not fill so full, therefore its output is reduced and this affects the left "heart" similarly. Therefore, unlike the river and dam, both pressure and flow are affected. If the "vessels" are quite rigid there is a good rise of pressure above the obstruction although flow is reduced also. But if the "vessels" upstream from the point of obstruction are easily distensible, flow will be affected much and pressure little if at all. Under similar conditions profound weakening of the right "heart" will likewise have almost no effect on "venous" pressure. The dam and stream analogy gives a false impression of simplicity to a physiologic situation which is in reality much more complex.

*Back-pressure.* An old clinical school of thought attributes the increased venous pressure of congestive heart failure to back-pressure from a weakened heart. The following example, a shortened form of that given by Harrison,<sup>7</sup> gives the mechanism of the rise of venous pressure according to this viewpoint. The left ventricle is expelling 40 cc. per beat. It weakens and then expels only 39 cc. For a short period the inflow into the left ventricle will continue to be 40 cc., and so, for a time, it receives more blood than it expels and slowly becomes dilated. While it is stretching, its internal diastolic pressure will rise, and, first the auricle, and finally the veins, will likewise receive more blood than is expelled from them, the pressure within them rising as their volume increases. This rising venous pressure increases the filling of the ventricle until its fibers, being more stretched, contract more strongly according to Starling's Law of the Heart. Therefore eventually the ventricle expels 40 cc. once more, as much as it receives. Equilibrium is now reestablished with the same cardiac output, the same arterial pressure, a larger diastolic heart size, and a higher venous pressure than before.

In our schema we have tried to reproduce this sequence of events by weakening one or both sides of the heart, but entirely without success. Diminution of flow and arterial pressure always accompanied the rise of venous pressure after the heart had been weakened. Reflecting on this failure we were forced to the conclusion that, while we could not deny that the changes described in Harrison's example might properly portray a train of events which may occur in clinical congestive failure, one could not regard cardiac weakness

as the direct mechanical cause of this train of events without invoking a mechanism inconsistent with the second law of thermodynamics. According to the examples cited, at the final equilibrium, the energy content of the circulation is higher than it was at the beginning; for venous pressure has risen and all else is the same as before. This *increase* in total energy cannot be the mechanical result of a temporary *decrease* of the energy imparted to the system by the heart.

*Analysis of the Increased Venous Pressure When Congestive Heart Failure is Simulated in the Schema.* When other factors were unaltered proportional weakening of both sides of the "heart" caused a rise of both "venous" pressures, a concomitant fall of both "arterial" pressures, and a diminished flow (Table 1). The pressure relations of congestive heart failure, increased systemic venous and normal systemic arterial pressure, cannot be reproduced by simply weakening the "heart" (Table 1, 1A and B) and this picture must be brought about by another or at any rate an additional mechanism. To discover it we first weakened the "heart" and then attempted by three separate maneuvers to restore "systemic arterial" pressure and so to reproduce the pressure relationships found in clinical congestive failure.

First, the pinchcocks on the "systemic" arteries were tightened. The "systemic arterial" pressure rose to normal, but "systemic venous" pressure fell back almost to its normal level, and flow was diminished still further (Table 1, 1C). So, clinical heart failure was still not simulated.

In a second attempt the "systemic" vessels were compressed from without over a considerable length. This maneuver increased "systemic" resistance as before and also, by forcing fluid into other parts of the system, raised the static pressure. Therefore, by suitable adjustment, "systemic arterial" pressure and flow could be restored to normal. In this case "venous" pressure remained elevated, and the pressure relations simulated clinical heart failure.

In a third attempt, additional fluid was added to the circulation. This also restored "cardiac output" and work, and "arterial" pressure to normal; and, as the static pressure was increased, the "venous" pressure remained elevated (Table 1, 1D). The effect of this maneuver was to simulate not only the pressure relations of clinical congestive failure, and the normal cardiac output demanded by Harrison's views,<sup>7</sup> but also the increased blood volume<sup>5</sup> and the increased static pressure found in this condition.

In our schema, to simulate the pressures found in clinical congestive heart failure, extracardiac forces which raise the static blood pressure are needed.

*Analysis of Certain Hydraulic Factors Concerned With One-sided "Heart Failure."* Experiments 2 and 3, Table 1, show the effects which follow one-sided heart failure in the schema.

Although the transference of fluid from the "pulmonary" to the "systemic" side, or vice versa, may be very conspicuous after mechanically obstructing the flow, this effect is small after weakening the right side of the "heart." There are two reasons for this: First, weakness of one "heart" always weakens the other also, so that the disproportion in strength is not as great as one would expect. Second, the volume of the "systemic" system is much larger than that of the "pulmonary" system. For this reason transference of a small percentage of the fluid in the "systemic" side to the "pulmonary" side affects the pressures in the smaller circuit profoundly, but a large percentage of the contents of the "pulmonary" circuit must be moved into the "systemic" side before much change in the "systemic" pressures occurs.

*The Relation of the Schema's Behavior to Certain Clinical Conceptions of Cardiac Failure.* Many authors<sup>4,7</sup> believe that, when a patient exhibits congestion of systemic veins, right-sided heart failure should be diagnosed. Similarly when the lungs are congested, the left heart is believed to be inadequate. That these two conceptions were not physiologically identical has not been realized.

The normal human lungs, with their capillary blood and a variable amount of their arterial and venous blood, weigh only about 1000 gm. at autopsy.<sup>17</sup> The heart and lungs of recently killed rabbits contain an average of 22.8% of the total blood volume.<sup>12</sup> By dye injections in man, Hamilton, Moore, Kinsman, and Spurling<sup>6</sup> estimate the volume of blood between the antecubital veins and the brachial artery to be about 2 liters normally; an estimate which includes the blood in the heart, in the systemic great veins, and in the systemic arteries to the point of puncture, in addition to the blood circulating in the lungs. When 500 cc. or more of blood is transfused into the systemic veins of patients without heart disease, the extra blood is doubtless distributed throughout the vascular system. The large proportion remaining on the systemic side causes no increase of venous pressure at all comparable with that found in congestive failure. Therefore we find it hard to believe that much of the increase of systemic venous pressure in congestive heart failure can be attributed to the transference to the systemic system of blood which could be spared from the lungs. On the other hand, it seems entirely reasonable to expect that transference of blood from the larger systemic to the smaller pulmonary side might be an important factor in the causation of the pulmonary congestion which has long been believed to follow failure of the left heart in clinical conditions.

Therefore we believe that weakness of the right heart, uncomplicated by any other physiologic changes, would not be followed by congestion of the systemic veins to the extent seen in congestive heart failure. However, if additional factors were present which had

previously increased static blood pressure, as an increase in blood volume or a general vasoconstriction might do, weakness of the right heart would have a much greater effect on venous pressure. For, in the first case, the blood transferred from the lungs would be accommodated in the flaccid systemic vessels with little increase of pressure; in the last, added to vessels already tense, it would increase the venous pressure much more.

The relation between right heart failure and systemic venous congestion is not as simple and direct as has been generally assumed when the one is so confidently diagnosed from the presence of the other.

**Conclusions.** A circulation schema is described whose pumps obey Starling's Law of the Heart.

On this schema the static blood pressure, *i. e.*, the pressure existing at all points in the circulation when the "heart" is stopped, is an important factor in compensation for weakness of the "heart" and in the causation of increased "venous" pressure.

The arterial and venous pressures of clinical congestive failure cannot be reproduced in this schema by weakening the heart alone. Mechanisms which cause an increase of static blood pressure, such as general vasoconstriction, pressure on vessels from without, or the insertion of additional fluid within the vessels, must be introduced before the pressure relations of clinical congestive heart failure can be reproduced.

The behavior of our schema has suggested clinical considerations which raised doubt in our minds whether the venous congestion of "congestive heart failure" was brought about in the manner commonly believed. This prompted the clinical investigation reported in the following paper.

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## RÔLE OF THE "STATIC BLOOD PRESSURE" IN ABNORMAL INCREMENTS OF VENOUS PRESSURE, ESPECIALLY IN HEART FAILURE.

### II. CLINICAL AND EXPERIMENTAL STUDIES.

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IN the preceding paper a schema of the circulation was described<sup>17</sup> which, we believe, mimicked physiologic conditions more closely than its predecessors. Studying the behavior of this schema we were impressed with the importance of the static blood pressure, *i. e.*, the pressure present throughout the circulation when the heart had stopped. For instance, after the heart had been weakened, mechanisms which raised static pressure had to be introduced before the arterial and venous pressures found in clinical congestive heart failure could be simulated. Also, increasing static blood pressure proved to be a method of partial compensation for weakness of the heart, for a measured weakening of one or both of the schema's "hearts" caused far less diminution of circulation when the static pressure was high than the same degree of weakening when this pressure was low.

Obviously, therefore, it seemed important to obtain data concerning the static blood pressure in clinical conditions. This was undertaken by making preparations in advance, waiting till the heart stopped at death, and then measuring this pressure by the introduction of a needle into a vein or, more conveniently, into the right ventricle. This measurement has been made in 64 patients with subsequent necropsies in about 70%.

The results show that cases dying with prolonged and severe congestive failure have a static blood pressure much higher than that found in persons dying of other causes. The differences found are sufficient to account for a large part, in some instances for all, of the differences in venous pressure found during life.

Therefore it appears that a large part of the force causing the increment of venous pressure in congestive failure is not derived directly from the heart for it persists when the heart is no longer functioning.

The author recalls an observation made when he was an intern, called to pronounce the death of a cardiac patient. With the body still supported on a back rest at 45°, the veins of the neck were distended as they had been during the last illness. I have repeated this observation many times since and do not doubt that many readers will recall the same fact. Therefore this investigation is but a quantitative study of a finding which may be familiar to many.

But I have found neither record of the fact nor discussion of its significance.

**Technique.** For measuring static blood pressure an 18-gauge needle,  $3\frac{1}{2}$  inches long, attached to a Luer-Kaufmann side-arm syringe was employed. The side arm was connected, through a T tube and pinchcocks, to a manometer of 3 mm. bore, and to a reservoir. The system was filled with either 0.9% NaCl or 0.5% sodium citrate. The heart, or occasionally a vein, was punctured and blood was drawn into the syringe until the side arm was opened. Then fluid was allowed to flow from the manometer as far as it would, care being taken that the syringe plunger was not drawn in as the pressure fell. This maneuver was repeated several times until the needle was washed free of blood and constant readings were obtained. The manometer was then lowered and the rise of the column to its previous level observed. Due to the viscosity of blood which now entered the long needle the level of the initial readings was often not attained with exactitude. The readings obtained with a falling column were considered correct, the attainment of approximately the same level by the rising column being regarded as a check on the patency of the system. A correction, made necessary by capillarity and by the force required to make fluid flow through needle and tubing, was applied to each reading. It amounted to almost exactly 1 cm. in my apparatus.

The apparatus was placed ready at hand, and I was notified as soon as death was pronounced. The great majority of the measurements were made within 30 minutes of that event. If death occurred at night the interns, after instruction in the technique, made the readings. The subject was always placed flat on his back when the estimations were made.

The plan of the investigation required repeated estimations of venous pressure on many patients. A large amount of the effort was lost, as measurement of static pressure did not always follow. Speed and convenience dictated the choice of method. The capsule methods soon proved too laborious for repeated estimations on different days. I finally came to depend on raising the hand and observing the level at which the veins filled and emptied, the method of Gaertner.<sup>9</sup> A small electric light (Bausch & Lomb whitelite transilluminator), attached to a flashlight battery, was laid on the skin beside the vein and the appearance or disappearance of the well marked shadow made the point of filling or emptying easy to identify. In addition, a direct measurement after venipuncture was made at least once on almost every patient, either using the apparatus described above, a technique adapted from that of Moritz and Tabora,<sup>14</sup> or simply connecting the needle to a small mercury manometer. This experience with several methods left me with a high regard for the rough accuracy of the Gaertner method, if carefully performed. But when patients were extremely dyspneic my results with the Gaertner technique were often somewhat too high and I soon learned to avoid this method under these circumstances. Fishberg<sup>8</sup> cites a similar experience.

There has been no agreement as to the proper base line for venous pressure measurements in recumbent patients. Clark, Hooker, and Weed<sup>5</sup> located the venous pressure reference point of dogs in the great veins. Also it seems evident that the static pressure of patients postmortem should be referred to the center of the body. Therefore to obtain a base line in supine subjects we measured the thickness of the thorax at the level of the junction of the sternum and the 4th rib and used the midpoint. Measurements made at necropsy in a number of cases indicated that this midpoint coincided with the level of the great veins.

Our principal interest in venous pressure concerned its relation to static pressure, so both measurements were referred to the same base line. There-



fore our figures for venous pressure are from 2 to 5 cm. higher than many results in the literature which have been measured from a level either one-third the distance from the anterior to the posterior chest wall, or 5 cm. below the anterior chest wall,<sup>7</sup> the position of the auricles.

Some patients died before venous pressure had been accurately measured. In these cases an impression of the amount the congestion has been recorded in general terms.

**Experiments Concerning Certain Properties of the Static Blood Pressure.** *Animal Experiments.* Although performed after the clinical investigation had been largely completed the results of the animal experiments can be presented best at this point, as they illuminate the clinical findings.

The ability of mammals to withstand hemorrhage and to receive intravascular infusions without much alteration in blood pressure is conspicuous and it has received much emphasis. Therefore it seemed proper to ask the question whether one had the right to expect that increased intravascular volume would raise venous and static blood pressures.

As no acute animal experiment can be designed to simulate clinical death, I attempted to safeguard the interpretation of the results by diversity in the experiments.

Dogs were employed. Tracheal, carotid, and femoral venous cannulae were inserted using great care to avoid blood loss. Venous pressures were estimated by allowing very small amounts of saline solution to run into a femoral vein from a manometer. The center of the dog's body was taken as base line.

In Dogs 1, 2, 3, and 4 the experiment was performed while the condition of the circulation was good. The dogs were injected with 2 mg. morphine per kilogram and then given intraperitoneally 1.5 cc. per kilo of a solution containing 2.8% of chloralose and 42% of urethane. After anesthesia and insertion of the cannulae, Dogs 1 and 2 received an intravenous infusion of Lilly's acacia diluted to make 6% acacia and 0.9% NaCl. Within 5 minutes after the infusion the dogs were killed by stabbing their hearts with a needle electrode and passing 110 volts D.C. through it. Dogs 3 and 4, having received nothing intravenously, were killed similarly after arterial and venous pressures had been recorded for a few minutes.

In Dogs 5, 6, and 7 similar experiments were performed after the blood pressure had been kept abnormally low for about  $1\frac{1}{2}$  hours by deep chloroform anesthesia. Dog 5 developed marked Cheyne-Stokes respiration with varying arterial and venous pressures. Dogs 6 and 7 were given acacia intravenously, Dog 5 serving as control. Dogs 5 and 6 were killed by excess anesthetic, Dog 7 was electrocuted.

The results are charted in Figure 1. In all but Dog 5 a period of struggle followed cessation of cardiac action and the gasping respi-

rations were accompanied by a great elevation of venous pressure which fluctuated with the muscular contractions. Quiet supervened in about 5 minutes and static blood pressure, similar in artery and vein, is recorded from that point. The curve obtained is very similar in all the animals. It descends from the high level reached in the struggle, and levels off about 20 minutes postmortem. After this the change does not exceed 1 cm. and the variation may be either up or down. Dogs 4, 5, and 7, followed for an hour postmortem showed no further change from that recorded. At the end of that time the blood had not clotted and the muscles contracted vigorously on electrical stimulation.

The form of the postmortem pressure curve in these dogs is similar to that found in rabbits by Riml.<sup>15</sup> The height of the curves of the control animals agrees well with the value found in rabbits by that author and with the average found in the control group of patients to be described.

The amount of acacia solution added, in per cent of the dog's probable blood volume, estimated as 7% of the body weight, is shown in Figure 1. It will be seen at once that, despite the diversity of the experiments, the results arrange themselves almost exactly in the order of the intravascular volumes. The interchange of position of the results secured in Dogs 1 and 7 may be due to differences in the condition of their circulations, or to differences in the anesthetic employed. It is, therefore, entirely proper to think of increased intravascular volume as a cause of increased static blood pressure.

The results obtained before the animals were killed indicate that increased intravascular volume can raise venous pressure also, as has long been known.<sup>16c</sup>

*Clinical Experiments.* These were performed postmortem before the blood clotted.

Case 33, apparently improving, collapsed while I was making ward rounds. Respiratory efforts persisted for about 5 minutes. Measurement of static blood pressure began 12 minutes postmortem. The results are charted in Figure 1 as curve A. The form of the curve is similar to that obtained in the animal experiments. Confirmation of the rapid fall occurring soon after death was obtained in another patient who died of pulmonary infarction during ward rounds. The static blood pressure was determined 10 minutes after death and fell about 1.5 cm. in the next 2 minutes when observations had to be discontinued.

No similar rapid change in pressure was found in any other case in the series. Evidently measurements began after the curve had leveled off. In 15 patients estimations repeated for an hour showed very little change with time. In one there was a fall at the rate of 1 cm. per 15 minutes. Changes in the other cases were smaller.

Slow drifts both downward and upward were seen, as in the animal experiments.

When the blood had clotted or rigor mortis had set in, the pressure within the circulation sometimes differed greatly from that obtained earlier. The change was in either direction. Values obtained so long postmortem, though often identical with those obtained earlier, are not to be trusted.

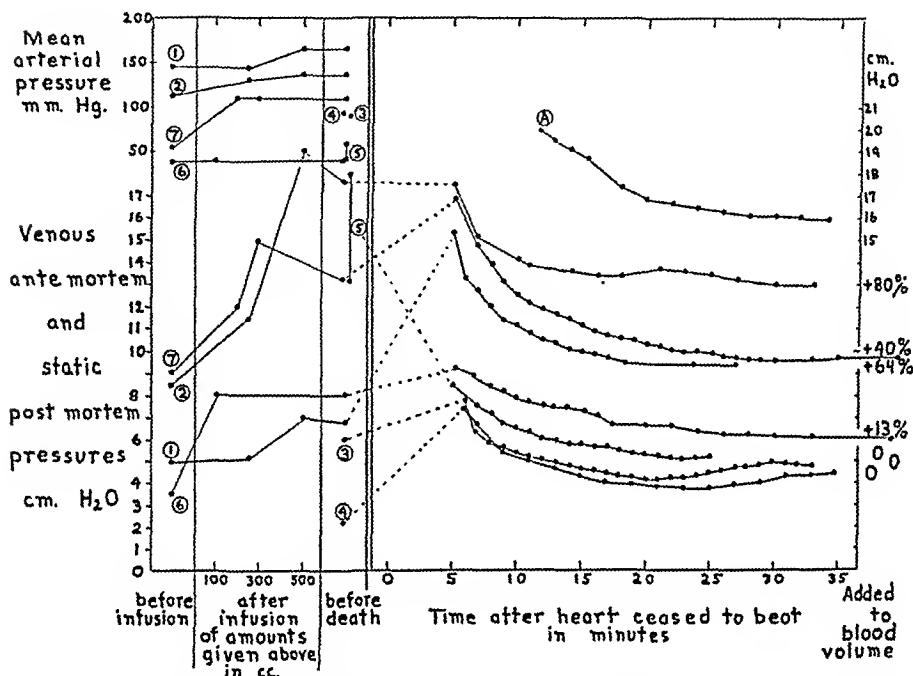


FIG. 1.—Results of animal experiments. The numbers correspond to the dogs mentioned in the text. Values charted to the left of the double line were obtained during life and represent arterial and venous pressures. Dogs 1, 2, 6 and 7 had intravenous infusions and the values obtained before, during, and after the infusions are recorded. To the right of the double line measurements of general static blood pressure are recorded at the time postmortem at which they were made. The first of these values is connected by a dotted line with the last value of the venous pressure obtained antemortem in the same dog. In the right hand margin is shown the amount of the infusion in per cent of the dog's probable blood volume calculated from his weight, for each animal. The curve A shows the change of general static blood pressure with time in Case 33.

Occasionally small rhythmic fluctuations in the static blood pressure made one wonder if all vital activity had ceased. Similar fluctuations were seen in the animal experiments. In a number of instances I attempted to demonstrate a persistence of vascular activity in the patients by injecting histamine and adrenalin into the skin. There was no visible response in any case.

Several experiments were made to throw light on the possibility that when the static pressure was high, it would diminish more rapidly in the period before measurement could be made because

blood was forced from the lifeless vessels at the higher pressures. In four experiments the static pressures were forced up by laying heavy weights on the abdomen, in one the same result was secured by injecting fluid into the peritoneal cavity. Thus in Case 7 this pressure, steady at 19.8 cm. for 19 minutes, was increased to 29.5 cm. by laying 20 lbs. on the abdomen. During the next 10 minutes it fell slowly to 27.6 cm., after removal of the weight it was 18.5.

In another experiment the static pressure changed from 10.57 to 13.8 on weighting the abdomen and remained unchanged at the higher level for 15 minutes. After removal of the weight the pressure was 9 cm. The other results were similar. Generally there was evidence of a slow drift downward at the higher pressures. But part of this effect may have been due to the expulsion of flatus by the abdominal compression, which was painfully obvious in most cases. Our evidence indicates that the rate of change is only slightly faster when the pressure is high. The results of the animal experiments permit a similar conclusion.

When the heart stops the pressures throughout the vascular system would equalize only if the vessels remained open. To safeguard ourselves on this point we twice made simultaneous estimations of pressure in a peripheral vein and in both ventricles, the position of the needles being verified at necropsy. We have also compared pressures in a peripheral vein and in the right ventricle in 11 cases. In all but 2 cases the agreement was within 1 cm. of water, a difference certainly within the error of the methods. In 2 cases differences between vein and heart pressures of 3.5 and 5.5 cm. are doubtless to be attributed to technical errors or to local venous obstruction. However experiments with a circulation schema containing a fluid of the same viscosity of blood<sup>17</sup> have shown that small differences in pressure may persist in different parts of the circulation for a long time after the pumps have been stopped.

Opening the vessels, as by the pathologist's incision, is followed immediately by diminution of static blood pressure. Intravenous injections raise this pressure. Thus in Case 32, with a static pressure of 9.5 cm. 150 cc. 5% acacia intravenously raised this pressure to 12 cm., a total of 295 cc. to 13.2 cm., 485 cc. to 14.4 cm., 635 cc. to 15 cm. These findings indicate that small changes in volume, such as might be due to the difference between the heart stopping in systole or diastole, or to the injection of small amounts of fluid in measuring the pressures, would have but little influence on our results. They also indicate that the larger increases in intravascular volume found in congestive failure<sup>10</sup> are sufficient to increase the static pressure to the value we find.

Pressure on the abdomen was followed by a prompt rise of static blood pressure. If the abdomen was flaccid this rise was small, if tense it was large. Thus in 1 case a weight of 40 lbs. laid on the flaccid abdomen increased the pressure 3.6 cm. In 2 cases whose

TABLE 1.—CLINICAL DATA.  
(Numbers in parentheses indicate the number of the day before death on which the observation was made.)

Case.	Age.	Sex.	B.P. (mm. Hg.).	Venous congestion		Static pressure (cm. H <sub>2</sub> O).	Remarks. Clinical diagnosis and pertinent necropsy findings.
				Duration (days).	Amount or pressure (cm. H <sub>2</sub> O).		
M. H. <sub>1</sub>	47	F	140/70	250	Moderate	21	<p><i>Group 1. Congestive Failure the Important Cause of Death.</i></p> <p>Rheum. ht. dis. aur. fib. Necropsy: chronic rheum. mitral and aortic valvulitis. Passive congestion of liver and lungs.</p> <p>Subacute Bact. Endocarditis. <i>Sircp. viridans</i>. Nec.: congenital septal defect, S.B.E. of all valves. Pass. cong. lungs, spleen, liver, etc.</p> <p>R.H.D. 4th attack of congestive failure. Mitral and aortic valvulitis. No nec.</p> <p>Nec.: chron. rheum. mitral and tricuspid valvulitis, pass. congest. lungs and abd. organs.</p> <p>B.U.N. 113. Uremia. Cardine hypertrophy and congestive failure. Nec.: (kidneys only) malign. nephrosclerosis.</p> <p>Diabetes since 1931. Nec.: Ht. 800 gm. Rheum. ht. dis. Coronary sclerosis, left-sided hypertrophy, right-sided dilatation. Phlebotomy 350 cc. before death.</p> <p>Luetie ht. dis. Aortic regurg. Rt. pleural effusion, tapped. Congest. ht. failure. No nec.</p> <p>Nec.: Advanced arteriolonephrosclerosis. Heart 330 gm. left vent. hypertrophy. 200 cc. fluid in pericardium. Massive hepatic necrosis.</p> <p>Terminal cardiac failure and uræmia. Nec.: chronic glomerulonephritis. Heart 350 gm. Pericardium coated with exudate, contains 200 cc. fluid. 2d estimate of V.P. made when patient's abdomen was greatly distended. There was no distention when the other estimates of V.P. were made.</p> <p>Nec.: chronic rheum. mitral and pan-valvulitis, active; myocardial dilatation. Passive congestion lungs and abd. viscera.</p> <p><i>Group 2. Congestive Failure Present at Some Time But Not the Chief Cause of Death.</i></p> <p>Nec.: malignant nephrosclerosis. Extreme edema of brain, edema and congestion of lungs, liver moderately congested. Heart 590 gm. L.V. hypertrophy. I did not see patient during life. This case perhaps belongs in Group 1.</p> <p>Urthral stricture and infected fistula. Edema and venous engorgement cleared up after treatment. Died after suprapubic cystostomy. Nec.: acute cystitis, nephrosclerosis. Ht. 800 gm., multiple infarcts, coronary sclerosis with occlusion, fibrinous pericarditis, hypertrophy, dilatation.</p> <p>Former hemiplegia. Hypertensive ht. dis. Pulmonary infarction. No nec.</p> <p>Asthma. Art. ht. dis. Coronary occlusion (?). No nec.</p> <p>Auricular fibrillation. Nec.: recent post. coronary occlusion, multiple infarcts of lungs. Received saline intravenously in large amounts up to 2d day before death.</p>
M. S. <sub>2</sub>	18	F	130/80	60	Marked	25	
J. McQ. <sub>3</sub>	26	M	130/70	3	Marked	17.5	
J. O. <sub>4</sub>	58	M	150/80	180	16 (1)	18	
N. B. <sub>5</sub>	37	M	238/158 (4)	14	36 (4)	23.5	
E. L. <sub>6</sub>	56	F	105/70 (1)	30	38 (1)		
G. C. <sub>7</sub>	28	M	125/95	30	20 (1)	18.2	
M. L. <sub>8</sub>	32	F	150/50	30	32 (0)	21	
P. R. <sub>9</sub>	40	F	178/128	5	Moderate		
W. E. <sub>10</sub>	30	M	190/110	21	11 (10)	20	
A. J. <sub>11</sub>	38	M	120/80	30	9 (6)		<p>Nec.: chronic rheum. mitral and pan-valvulitis, active; myocardial dilatation. Passive congestion lungs and abd. viscera.</p> <p><i>Group 2. Congestive Failure Present at Some Time But Not the Chief Cause of Death.</i></p> <p>Nec.: malignant nephrosclerosis. Extreme edema of brain, edema and congestion of lungs, liver moderately congested. Heart 590 gm. L.V. hypertrophy. I did not see patient during life. This case perhaps belongs in Group 1.</p> <p>Urthral stricture and infected fistula. Edema and venous engorgement cleared up after treatment. Died after suprapubic cystostomy. Nec.: acute cystitis, nephrosclerosis. Ht. 800 gm., multiple infarcts, coronary sclerosis with occlusion, fibrinous pericarditis, hypertrophy, dilatation.</p> <p>Former hemiplegia. Hypertensive ht. dis. Pulmonary infarction. No nec.</p> <p>Asthma. Art. ht. dis. Coronary occlusion (?). No nec.</p> <p>Auricular fibrillation. Nec.: recent post. coronary occlusion, multiple infarcts of lungs. Received saline intravenously in large amounts up to 2d day before death.</p>
C. J. <sub>12</sub>	58	M	250/140	Unknown	23 (1)		
N. S. <sub>13</sub>	52	M	130/90	Temporary 3	None recorded	19.5	
S. D. <sub>14</sub>	70	M	185/120	1	25 (8)		
A. Z. <sub>15</sub>	63	F	100/30 (1)	Transient 7	11 (6)		
			130/72		16 (2)		
					11 (1)		
					Slight		
					13 (1)		
					18 (12)		
					21 (8)		
					14 (4)		
					14 (3)		

T. O'N. 16	50	M	214/140	Transient 21	23 (50) 22 (31) 11 (17) Slight	15 13.3	Congestion cleared up under treatment, finally died of uremia and terminal erysipelas. Nec.: malignant arteriolonephrosclerosis. Ht. 755 gm. L. V. hypertrophied, fibrinous pericarditis.
D. D.F. 17	56	M	120/70	Terminal event 1	23 (2)	16	Angina pectoris. Cardiac silhouette + 100%. Auricular fibrillation. Old infarct? No nec.
A. W. 18	56	F	190/60	Transient 2	13 (17) 41 (2) 19 (13) 15 (2) 14 (1)	16	Chronic arteriolonephrosclerosis, cardiac hypertrophy, auric. fib., uremia. Received 1000 cc. saline daily by vein. No nec.
A. K. 19	45	F	250/155	Terminal event 2	27.5 (2)	14.5	Chronic glomerulonephritis with uremia. Cardiac hypertrophy, orthodiagram + 53%. No nec.
D. S. 20	68	F	170/90 (5)	Transient 10	None	7.5	Admitted in congestive failure which cleared up under treatment. Died from encephalitis from an infected sinus. Hypertensive ht. dis. Cardiac hypertrophy. Aur. fib. No nec.
O. G. 21	50	M	130/50 (1) 100/110 (3) 105/65 (2)	Terminal event 2	11 (1) 13 (3) 11 (3) 8 (3) None	14.5	Nec.: heart 670 gm. Marked hypertrophy, coronary sclerosis. Cerebral arterioscl. with ventricular hemorrhage.
H. S. 22	39	M	120/70	...	15 (1)	16	Group 3. Cases of Heart Disease Dying Without Edema or Congestion.
I. F. 23	20	F	120/72 70/55 (1)	...	None observed	0.5	Nec.: chron. rheum. valvulitis, subacute bacterial endocarditis, metastatic encephalitis with cerebral hemorrhage. Passive congestion of lungs and abdominal viscera.
L. P. 24	53	M	124/80	...	11 (1)	9	Old rheum. ht. dis. Sub. bact. endocarditis, cerebral embolism. No nec.
R. T. 25	70	F	190/100	...	13 (3)	7.5	Bronchial asthma. Art. ht. dis. cong. failure in 1934, recovered. Nec.: (1936) Ht. 700 gm., extreme hypertrophy, myocardial infarct with mural thrombosis. Thrombosis basilar artery of brain. Bronchopneumonia.
J. M. 26	58	M	90/70	...	8 (3)	7.5	Hypertension known 2 yrs. Fell unconscious. Ht. enlarged. Aur. fib. Diagnosis cerebral hemorrhage. No nec.
K. D. 27	47	M	130/75	...	None	12	Sudden precordial pain. Diagnosis acute myocardial infarction, ant. wall left vent. No nec.
H. F. 28	65	F	130/75	...	7 (0)	13	In cong. failure 1934, recovered. In 1936 fever and purpura. Nec.: acute necrotic enteritis, ht. 470 gm., rheum. mitral valvulitis, hypertrophy, mod. coronary sclerosis.
M. B. 29	41	F	120/75	...	None	14.5	Nec.: multiple myeloma, bronchopneumonia. Ht. 360 gm., old rheum. valvulitis. Nec.: adenocarcinoma of lung. Ht. 260 gm. 250 cc. bloody pericardial fluid, metastatic pericardial adenocarcinoma, active rheum. mitral valvulitis. Passive cong. of liver.
J. B. 30	41	M	100/60	...	None	9.5	Old angina pectoris. Severe precordial pain, in shock when V.P. was measured. Nec.: Ht. 430 gm. Multiple coronary occlusions with myocardial infarcts. Marked coronary sclerosis.
L. B. 31	35	F	216/164	...	12 (7) 12 (5) 12 (3)	9.5	Nec.: malignant nephrosclerosis. Ht. 350 gm. L.V. hypertrophy, fibrinous pericarditis, marked coronary sclerosis.
J. J. 32	63	M	130/80	...	None recorded	16	Diabetes mell. Legs amputated, last in 1935. Infection of stump. Nec.: (1936) cellulitis of stump, terminal septicaemia. Heart: Septic thrombosis rt. auricle, mod. coronary sclerosis.
S. G. 33	20	M	215/130	...	None	10	Died suddenly. Nec.: chronic glomerulo-nephritis. Pul. edema. Pass. cong. of liver and spleen. Edema of brain. Ht. 505 gm. L.V. hypertrophied.
J. E. 34	36	M	130/70	...	None	6.5	Congestive failure 1935, recovered. Auric. fib., jaundice, fever, cholecystostomy. Died 2 mos. postop. Nec.: chron. rheum. mitral valvulitis, cholecystitis, hypertrophic cirrhosis, terminal septicaemia with ulcerative endocarditis.
L. P. 35	40	M	120/80	60?	R 45 (3) L 58 (3) R 48 (1) L 58 (1)		Group 4. No Cardiac Disease.

Group 4. No Cardiac Disease.

Venous pressure measured both arms. No congestion of leg veins. Nec.: primary bronchogenic carcinoma, mediastinal metastasis obstructing superior vena cava, multiple visceral metastases.

Remainder of this group, see Table 2.

abdomens were more tense 20 lbs. increased this pressure 7.3 and 9.8 cm. In 1 distended case 40 lbs. elevated this pressure 17 cm. The rapid response of the manometer to pressure on the abdomen proved a handy way of assuring oneself that manometer fluid and blood were in pressure equilibrium.

*Arrangement and Results of the Clinical Study.* The 64 cases have been divided into 5 groups. Pertinent data concerning clinical and necropsy findings and the results of measurements of venous and static pressures in these cases have been given in Table 1. Figure 2 summarizes the static pressures.

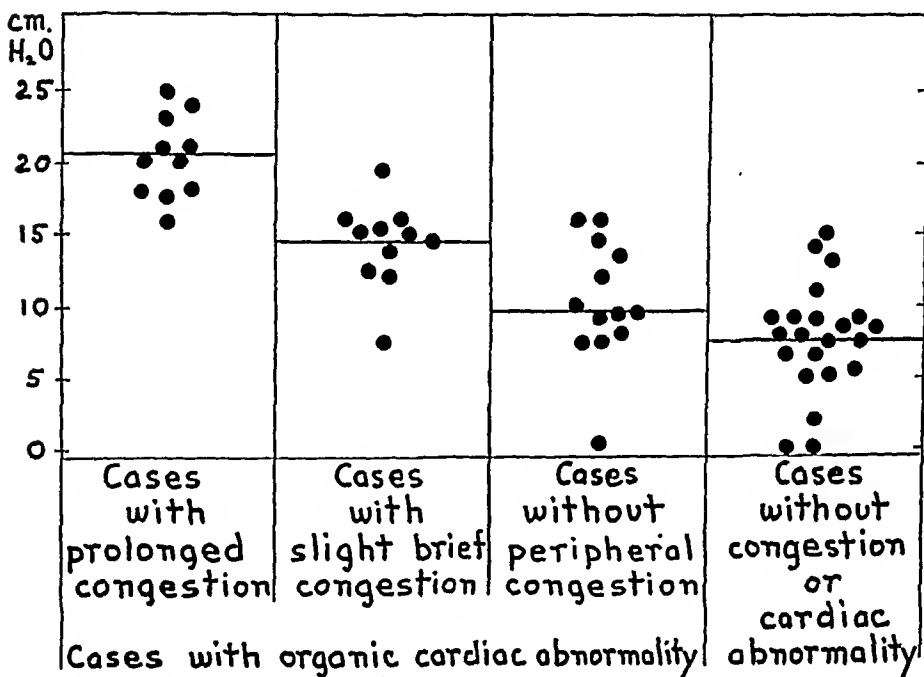


FIG. 2.—The static blood pressures in various groups of cases. The cross bars indicate the average values. The mean of Group 1 is significantly different from the means of Groups 3 and 4 (for  $P = 0.05$ ), and it just fails to attain a similarly significant difference from Group 2. The means of Groups 3 and 4 are not significantly different from each other.

The cases placed in the first three groups all had some organic cardiac abnormality. In Group 1 have been placed 10 cases in which congestive heart failure was judged to be a major, if not the sole, cause of death. In Group 2 have been placed 11 cases in which congestive failure was present at some time during the course of the disease but it either cleared up before death or appeared to be a brief terminal event in patients dying from another cause.

In Group 3 have been placed 13 cases in whom neither venous congestion, nor "cardiac" edema was observed at any time during life. However, in Cases 22 and 29, passive congestion was demon-

strated at necropsy and this was doubtless the factor which made their static pressures the highest of the group. If these 2 cases are promoted to Group 2 the average static pressure of Group 3 is reduced from 9.7 to 8.4 cm.

Group 4, the control group, consists of 25 cases characterized by essentially normal hearts. Their static pressures average 7.2 cm. (Table 2).

TABLE 2.—COMPARISONS OF VENOUS CONGESTION (ANTEMORTEM) AND STATIC PRESSURES (POSTMORTEM) IN PATIENTS WITH NORMAL HEARTS.

Case.	A.M. venous congestion or pressure (cm. H <sub>2</sub> O).	P.M. static pressure (cm. H <sub>2</sub> O).	Necropsy.	Chief diagnosis and remarks.
<i>Group 4. No Cardiac Disease.</i>				
J. M. . . . .	14	14	Yes	Myel. leukemia; recurrent as- cites
M. M. . . . .	None	2	Yes	Polyposis of colon; anemia
J. H. . . . .	None	9	Yes	Ca. pancreas
F. D. . . . .	None	15	Yes	Ca. esophagus
J. S. . . . .	None	7.5	Yes	Cholelith., peritonitis
W. A. . . . .	None	5	Yes	Ca. of tongue
S. P. . . . .	None	5	Yes	Meningitis
S. C. . . . .	None	8	No	Chronic nephrosis
A. R. . . . .	None	8	Yes	Strep. pneumonia
W. A. . . . .	9	8.5	Yes	Meningitis
F. W. . . . .	10	0	Yes	Pul. tuberculosis, purpura
C. W. . . . .	13	9	Yes	Bronchopneumonia
J. W. . . . .	10	11	Yes	Lymphosarcoma
A. C. . . . .	None	9	Yes	Ca. gall bladder
M. S. . . . .	None	6.5	Yes	Ca. breast
C. B. . . . .	10	9	Yes	Diabetes mel. septicemia
J. R. . . . .	11	0	Yes	T.B. meningitis
A. M. . . . .	15	8.5	Yes	Lobar pneumonia (distended when V.P. was taken, not at death)
R. O. . . . .	5.5	7.5	No	Meningitis
J. O. . . . .	8	13	No	Bronchopneumonia
K. W. . . . .	None	5.5	Yes	Lung abscesses
J. D. . . . .	15	0	Yes	Empyema
P. P. . . . .	8.5	7.5	No	Ca. lung
J. P. . . . .	10	7	No	Ca. stomach
L. P. . . . .	..	..	..	See Table 1, Case 35
<i>Group 5. Cases Dying With Marked Abdominal Distention.</i>				
M. O. . . . .	..	23	Yes	Lobar pneumonia
F. A. . . . .	..	19	No	Lobar pneumonia
X. S. . . . .	..	13.5	Yes	Myel. leukemia, hemorrhage
I. D. . . . .	..	14.5	Yes	Gen. peritonitis

In a special fifth group have been placed 4 cases; their data will be found in Table 2. Each of these died with marked abdominal distention. The static blood pressures were high in this group, averaging 17.2 cm., a result consistent with the observation that when intraabdominal pressure is increased intentionally the static blood pressure rises.

Figure 2 shows the individual and average static blood pressures in the first four groups. Obviously the static pressure may have been influenced by the treatment employed in several cases. When transfusion or venesection was employed as a last resort this is noted in the tables. Slow intravenous saline infusions were used occasionally and, thinking that the resulting pressure changes would be small and transient, we have included these data.



**Discussion.** *Certain Fundamental Difficulties and Assumptions.* One must ask whether the static blood pressure obtained postmortem truly represents the corresponding pressure present during life. The results of experiments on animals bear on this question. Starling,<sup>16a</sup> after sectioning the cord to prevent asphyxial vasoconstriction, stopped a dog's heart by stimulating the vagus. Three minutes later the blood in arteries and veins was in pressure equilibrium at 8.3 cm. H<sub>2</sub>O. After the curve had leveled our control dogs showed an average postmortem blood pressure of about 5 cm. H<sub>2</sub>O (Fig. 1). But section of the cord affects vascular tone and the experiments may not be comparable.

When I stopped the heart by stimulating the vagus,<sup>16a</sup> an experiment I tried repeatedly in Dogs 1 and 2, struggle and asphyxial vasoconstriction supervened before the pressures in arteries and veins equalized. So I was unable to discover a level during life which could be compared with that found postmortem.

The expectation is that, because of vascular and muscular relaxation, the static pressure diminishes postmortem. Therefore the value obtained when it has become stationary is probably somewhat smaller than the corresponding pressure present before death. But the change is probably much smaller than the difference between the initial and final postmortem pressures shown in Figure 1. Asphyxial vasoconstriction and muscular activity were undoubtedly factors in the values first obtained in these experiments.

Conclusions must be drawn on the assumption that the change in static pressure is equal, on the average, in the various groups of patients, so that the differences found after death represent differences present during life. This assumption is supported by the results of the experiments on dogs (Fig. 1). The falling postmortem pressure curves remain discrete and arrange themselves nearly in the order of the intravascular volumes present during life.

However, in the patients whose static blood pressures were forced up postmortem, the elevated curves diminished somewhat faster than the lower ones. The animal experiments showed a similar result. Therefore the differences found postmortem in our cases may somewhat underestimate the differences present during life.

The objection might be raised that some special feature of congestive failure, associated with death by slow failure of the circulation, might prevent the drop of the postmortem pressure curve in these cases and so account for the differences found. One can only point out that lack of oxygen would be expected to increase capillary permeability in congestive failure, and that the cases of coronary thrombosis in Group 3, also dying with gradually failing circulations, showed no comparable elevation of static blood pressure. Cases of heart disease, dying without congestion, do not have high static pressures.

It seemed possible that the height of the blood proteins might

influence the results by controlling the rate of diffusion of fluid from the blood. Blood proteins had been estimated before death in 12 patients, the results ranging from 3.6 to 6.7%. When these figures were plotted against the corresponding static pressures the points were so widely scattered that it seemed evident that the amount of blood proteins was no important factor in our results.

*Interpretation of the Results.* The behavior of the circulation schema permits one to classify the factors which may increase venous pressure as:

Group 1. Factors causing transference of blood from arteries to the veins. Cardiac weakness, slowing of the circulation from any cause, or diminution of peripheral resistance, would bring about effects of this kind.

Group 2. Factors causing transference of blood from the systemic to the pulmonary system, or *vice versa*. Weakening only one side of the heart relative to the resistance it must overcome, while the strength of the other remained intact, would cause effects of this kind.

Group 3. Factors causing increased static pressure; due to (a) increased intravascular volume sufficient to stretch the vessel walls, (b) vasoconstriction, or (c) pressure on blood-containing vessels from without. Unlike the factors in Groups 1 and 2, the agents which bring about such changes of static pressure are not immediately connected with the heart. If there is any connection it must be a remote one with steps in between.

Factors of Groups 1 and 2 cause readjustments inside the circulation. They are directly due to the heart and when the heart stops all evidence of their previous presence disappears. They do not affect static pressure. The factors in the last group are not directly due to the heart and they cause an increment of pressure which persists after the heart has ceased to beat.

Since cases of congestive failure have a higher static pressure after death than controls it seems obvious that factors of the third group must have entered into the increment of venous pressure present during life. The next question is, what percentage of this venous pressure increment can be properly attributed to these factors?

The static pressure in cases dying in congestive failure averages 20.7 cm. of  $H_2O$ , in cases dying without heart disease it averages only 7.6 cm., the difference is 13.1 cm. of water. According to Eyster<sup>7</sup> the venous pressure of normal persons is from 4 to 6 cm.  $H_2O$ , this pressure in the 6 cases of cardiac decompensation given in his Table 1 averages 19 cm., 14 cm. above the normal average. Villaret *et al.*,<sup>18</sup> measuring from a different base line, call the normal venous pressure 13 and 12 cm.  $H_2O$  for men and women, respectively. In the 7 cases of congestive failure reported the average venous pressure was 28 cm., 15.5 cm. above the normal average. Our

results are very similar. Apparently the average difference between the static pressures is sufficient to explain over 85% of the average increment of venous pressure found in congestive failure.

But in certain individual cases the results point to a different conclusion. In Cases 5, 19, and 21, all with hypertension, the elevation of static pressure will explain less than half of the venous pressure increase found during life. In Case 35, with mediastinal obstruction of the veins, the static pressure played no part at all in a maximum rise of venous pressure. Obviously other factors were operating in these cases. On the other hand, in the case of mitral stenosis, Case 10, in which right-sided failure might have been diagnosed, and the presence of the cardiac factors of Groups 1 and 2 expected, the static pressure accounted for all the increment of venous pressure.

Returning to the discussion of the average results one may ask what causes the average increment of static pressure in congestive failure. One factor is surely the increased blood volume found in this condition, a view put forward by Bolton<sup>2</sup> from results of animal experiments to be described. A relationship between venous pressure and blood volume in clinical congestive failure has been demonstrated by Brandt<sup>3</sup> and, using better methods, by Gibson and Evans<sup>10</sup> who review the other literature consistent with this conception.

Certainly other factors may contribute to the increment of static pressure in certain cases. Pressure exerted on vessels from without, as by edema or fluid in the body cavities, would also cause increased static blood pressure persisting after death, if there were no compensatory decrease of blood volume. The results obtained in the 4 cases of Group 5 who died with extreme abdominal distention give evidence that such factors exist. Their static pressures averaged 9.6 cm. above the average normal level although their hearts were normal. Also I have observed the venous pressure to increase markedly when distention was present (Case 9) and to diminish as soon as it was relieved. Clark<sup>4</sup> found venous pressure to diminish after tapping the chest in 7 of 8 cases and he described the relation of venous pressure and urine volume as inverse and coincident in 6 cases of congestive failure. We have similar data in 5 cases. These results are consistent with the view that fluid or gas in the body, sufficient in amount to compress the adjacent vessels, is a factor in the elevation of the static, and so of the venous, pressure.

General vasoconstriction or increased muscular tone<sup>12</sup> would certainly be a factor in the static pressure. It is impossible to say definitely how much vital factors of this kind contribute to the static pressure as we measure it postmortem. One is tempted to think that muscular relaxation causes the fall which occurs during the 15 or 20 minutes after the circulation has stopped, and that the leveling after that time indicates that vital activity has largely ceased. But strips of human arteries, obtained at amputation by

Cow,<sup>6</sup> when placed in oxygenated Ringer's solution at 37°, maintained their power of reaction to stimulæ for several hours without impairment. On the other hand, neither adrenalin nor histamine, injected into congested areas of skin when non-cardiac pressure was measured, caused any visible response in several of my patients.

The sum of the results given above drives one to attribute the largest part of the venous pressure increment in most cases of congestive failure to factors such as increased blood volume and pressure on the blood in the vessels by fluid or gas within the body. Our data shows that other factors are more important than these in only a few cases.

*The Relation of Our Results to Conceptions Derived From Animal Experiments.* Starling<sup>16a</sup> attempted to simulate cardiac failure in animals by injecting oil into the pericardium. The results led him to develop the mechanical theory of edema formation which bears his name. As a logical deduction from this theory he wrote, in 1896, "A condition of hydræmic plethora must be an inevitable physiological consequence of the failure of the heart pump." Starling believed that both plethora and vasoconstriction elevated the static blood pressure in heart failure and that they were factors in the increased venous pressure characteristic of this condition.

Bolton<sup>2</sup> attempted to reproduce the effects of heart disease in cats. In early experiments he diminished the circulation by constricting the pericardium, later he narrowed the superior and inferior venæ cavæ at their entrance to the heart, and finally, he found that the same effects could be produced by narrowing the inferior vena cava alone. Ascites soon followed this operation. Edema appeared early and persisted in the area drained by the obstructed vein. Venous pressure in this same area rose a little immediately after the operation and this was attributed to slowing of the blood stream and to piling up of blood behind the obstruction. A few hours later it fell to normal but then rose as the arterial pressure recovered. This second rise of venous pressure was attributed to vasoconstriction. About a week after the operation the cats began to increase their blood volumes, as estimated by the "wash out" method. The venous pressure in the area of obstruction rose coincidentally to a high level. This increase was attributed to the plethora. Excess of fluid intake over urine output was observed. The blood was at first diluted but later regained its usual concentration although plethora continued. Ten to 17 weeks after operation increments up to 40% of blood volume were found.

These experiments have received little attention by clinicians, possibly because of a natural hesitation in granting that partial obstruction of the inferior vena cava was truly analogous to failure of the heart muscle. But from the results of these animal experiments Starling<sup>16b</sup> and Bolton<sup>2</sup> developed a viewpoint of congestive failure the main features of which my results uphold.

Our data indicate that the systemic venous congestion of congestive heart failure is not fully explained as the direct mechanical consequence of weakness of either the right heart or the whole heart. Our evidence indicates that, while increments of venous pressure directly due to cardiac weakness exist, they are minor factors in the clinical pictures of most cases. Therefore the largest part of the venous pressure increment of congestive failure is not directly due to the heart. But these observations give no basis for denying that there might be an indirect relationship with physiologic steps in between. They are consistent, with the finding of normal cardiac output in some cases of congestive failure,<sup>1,11</sup> and with the view, recently supported by McMichael's data,<sup>13</sup> that venous congestion represents an effort on the part of the body to compensate for weakness of the myocardium by increasing the heart's filling pressure.

But we must not forget that the evidence relating venous congestion to cardiac dysfunction has been weakened by these data. One can now readily conceive of types of venous congestion which might originate from disease of other organs than the heart.

**Conclusions.** The pressure remaining throughout the circulation after the cessation of cardiac action, the "static blood pressure," has been measured promptly after death in 64 patients. Necropsies were performed in 44 of these cases.

In persons dying of prolonged congestive heart failure the static blood pressure averaged 20.3 cm. H<sub>2</sub>O. In persons dying without heart disease it averaged 7.6 cm. This difference is large enough to account for the major part, in some instances for all, of the high venous pressure found in cases of congestive failure during life.

Obviously, therefore, the larger part of the increase of venous pressure found in congestive failure should not be attributed directly to any difference of cardiac function, for the abnormality persists when the heart is no longer functioning.

Well known theoretical conceptions in congestive failure have been restudied and reassessed in the light of this new information.

I am indebted to numerous members of the Department of Pathology, especially to Dr. O. Norris Smith, for permission to use their necropsy findings and for the performance of certain special studies at my request. The high percentage of necropsies in my cases was due to the skill and energy of the medical residents, Drs. H. F. Flippin and A. W. Terrell, who also assisted the investigation in numerous other ways. My records contain the names of the following interns who made estimations of non-cardiac pressure at night and assisted me in various ways: Drs. W. Jaquette, D. N. Stewart, F. M. Thigpen, W. P. Stewart, T. Lovitt, J. L. Morrison, D. MacL. Wilson, D. Z. Rhoads, J. P. Atkins, L. R. Twyeffort, T. E. Machella, J. G. Smith, H. G. Scheie, A. J. Gaydosh, and R. E. Hobler.

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## THE TREATMENT OF PNEUMOCOCCUS PNEUMONIA: A COMPARISON OF THE RESULTS OBTAINED WITH SPECIFIC SERUM AND WITH SULFAPYRIDINE.

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In the short time since Evans and Gaisford<sup>2</sup> made the first report of the treatment of 100 cases of pneumococcus pneumonia with sulfapyridine, many investigators have attested to the favorable influence of the drug in decreasing the mortality rate and shortening the clinical course of the disease. The various publications to date have been chiefly concerned with the shortening of the febrile period and the reduction in the mortality rate of the disease, and with the toxic effects of the drug. In general, investigators have obtained mortality rates as favorable as those heretofore reported following the use of specific serum. Actual comparison of the value of sulfapyridine and serum in the treatment of pneumonia has received but slight attention. Therefore, we have attempted to obtain answers to two questions:

1. When comparable groups of cases are treated over the same period of time, will sulfapyridine or will serum be more effective in altering the course of the disease and its mortality rate? and

2. Are there any special situations in which one agent is superior to the other?

From September 1, 1938, through July 15, 1939, 226 cases of pneumonia were treated by us. Of these patients, 90 were given serum alone, 130 sulfapyridine alone, and 6 received both drug and serum. Most of the patients were treated in conjunction with the

Pneumonia Control Program of the Health Department of the District of Columbia in the wards of Gallinger Municipal Hospital and other hospitals of Washington or in homes, while a few were private patients seen in consultation by either of us. The series includes all the adult patients with pneumococcus pneumonia treated by us during this period, no cases having been excluded.

Typing of each patient's sputum was performed at least once and often several times. One or more blood cultures and Roentgen rays were taken on nearly every patient. In addition, cultures were made of all exudates and from the lungs at postmortem.

From August 1 until November 17, 1938, before sulfapyridine became available, patients were treated with serum\* alone. After that date, the Type I cases were alternated, one being given serum and the next the drug. When a serum for a particular type was on hand it was used; otherwise the patient was treated with sulfapyridine. There was no selection of cases on the basis of severity, except that both serum and sulfapyridine were given to 6 extremely ill patients.

**Results of Treatment.** In Table 1 are shown the results of treatment with each of these two therapeutic agents. Pneumonias caused by each type of pneumococcus are listed separately, and, in addition to the total for all types, a sub-total has been calculated for Types I, II, V, VII and VIII pneumonias. The reasons for these types of pneumonias being considered especially suitable for the present comparison are enumerated in the Discussion. Purely for the sake of brevity these pneumonias will be spoken of as the "lower-type" pneumonias.

**Mortality Rates.** *Types I, II, V, VII and VIII.* Among the 70 "lower-type" pneumonias treated with serum, there were 10 deaths (14.3%). There were 5 deaths among the 52 patients treated with sulfapyridine (9.6%). The 4 individuals treated with a combination of serum and sulfapyridine were severely ill patients; all of them died.

When only the bacteremic cases are considered, it will be seen that there were 3 deaths among 17 patients treated with serum and the same number among 16 patients treated with the drug. The mortality rates are therefore similar: 17.7% for serum-treated and 18.8% for sulfapyridine-treated cases.

Clinicians have long observed that the most effective results are obtained when serum treatment is begun during the first 4 days of the illness. This was true in the present series (as in Table 1) where the mortality rate for patients receiving their first dose of serum during this early period was 10.8%. Early treatment was even more effective in the sulfapyridine-treated cases. The mor-

\* Serums for some of the "higher" types were available for testing through the courtesy of the Lederle Laboratories, Inc., and the Gilliland Laboratories, Inc.

tality rate was only 2.9% among the 34 patients receiving sulfapyridine during the first 4 days of the illness.

TABLE 1.—EFFECT OF SPECIFIC SERUM OR SULFAPYRIDINE ON MORTALITY IN PNEUMOCOCCUS PNEUMONIAS.

Type of pneumococcus.	Serum.									Sulfapyridine.								
	All cases.			Bacteremic cases.			Cases treated in first 4 days.			All cases.			Bacteremic cases.			Cases treated in first 4 days.		
	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.
I	31	3		8	1		26	3		23	0		7	0		18	0	
II	<sup>6</sup> 4 <sup>1</sup>	<sup>2</sup> 1		0	0		5	1		<sup>6</sup> 4 <sup>1</sup>	<sup>2</sup> 1		2	1		3	1	
V	4	0		1	0		3	0		2	0		0	0		1	0	
VII	15 <sup>1</sup>	1 <sup>1</sup>		4 <sup>1</sup>	1 <sup>1</sup>		5	0		11 <sup>1</sup>	1 <sup>1</sup>		4 <sup>1</sup>	1 <sup>1</sup>		5	0	
VIII	14 <sup>2</sup>	4 <sup>2</sup>		4 <sup>1</sup>	1 <sup>1</sup>		7	1		10 <sup>2</sup>	2 <sup>2</sup>		3 <sup>1</sup>	1 <sup>1</sup>		7	0	
Subtotal	70 <sup>4</sup>	10 <sup>4</sup>	14.3	17 <sup>2</sup>	3 <sup>2</sup>	17.7	46	5	10.8	52 <sup>4</sup>	5 <sup>4</sup>	9.6	16 <sup>2</sup>	3 <sup>2</sup>	18.8	34	1	2.9
III	6	1		1	1		3	1		25	1		3	1		15	1	
IV	5 <sup>1</sup>	1 <sup>1</sup>		0	0		3	1		9 <sup>1</sup>	1 <sup>1</sup>		2	0		6	0	
VI	2	0		0	0		1	0		2	0		0	0		2	0	
IX	1	1		1	1		1	1		4	0		0	0		3	0	
X	—	—		—	—		—	—		3	0		0	0		0	0	
XI	—	—		—	—		—	—		2	0		0	0		2	0	
XII	3	0		1	0		1	0		3	0		0	0		1	0	
XIII	—	—		—	—		—	—		3	0		0	0		2	0	
XIV	1	0		1	0		1	0		6	1		0	0		2	0	
XV	—	—		—	—		—	—		2	0		0	0		1	0	
XVI	—	—		—	—		—	—		2	1		0	0		1	0	
XVII	1	0		0	0		—	—		1	0		1	0		0	0	
XVIII	—	—		—	—		—	—		6	1		2	0		2	0	
XIX	4	2		0	0		2	0		3	1		0	0		1	0	
XX	—	—		—	—		—	—		1	0		0	0		0	0	
XXI	—	—		—	—		—	—		3	1		0	0		3	1	
XXII	—	—		—	—		—	—		3	3		1	1		0	0	
XXIII	1	1		0	0		1	0		—	—		—	—		—	—	
XXIV	—	—		—	—		—	—		2	0		0	0		1	0	
XXVII	1	0		0	0		1	0		3	0		0	0		2	0	
XXXI	1 <sup>1</sup>	0		0	0		0	0		1 <sup>1</sup>	0		0	0		0	0	
Total	96 <sup>6</sup>	16 <sup>6</sup>	16.7	21 <sup>4</sup>	5 <sup>4</sup>	23.8	60	8	13.3	136 <sup>6</sup>	15 <sup>6</sup>	11	25 <sup>4</sup>	5 <sup>4</sup>	20	78	3	3.8

\* Cases denoted by superscripts were treated with serum and sulfapyridine combined.

In order to determine the relative severity of the disease in the serum- and sulfapyridine-treated groups, they are compared in Table 2 with respect to age, amount of lung involvement and presence of bacteremia. Among the patients treated with serum, only 18.6% were over 40 years of age, while 36.5% of the sulfapyridine cases were in this age group. More than one lobe was involved in a slightly higher percentage of patients among the serum-treated group (35.7%) than among the sulfapyridine-treated group (30.8%).



One or more positive blood cultures were obtained from 26.6% of the serum-treated patients as compared to 33.3% of the patients treated with sulfapyridine. It will be seen from the above data that the groups of cases treated by the two agents were about equal in severity. More of the sulfapyridine-treated cases were over 40 and were bacteremic; more of the serum-treated cases had extensive involvement.

TABLE 2.—THE EFFECT OF CERTAIN FACTORS UPON MORTALITY RATE IN PNEUMONIAS TREATED WITH SERUM OR SULFAPYRIDINE (TYPES I, II, V, VII, VIII).

		Serum.			Sulfapyridine.		
		No.	Died.	Mortality, %.	No.	Died.	Mortality, %.
Effect of age	12 to 40	57	4	7.0	33	2	6.1
	Over 40	13	6	46.2	19	3	15.8
	% over 40	18.6	—	—	36.5	—	—
Effect of area of lung involved	1 lobe	45	1	2.2	36	2	5.5
	More than 1 lobe	25	8	32.0	16	3	18.8
	% more than 1 lobe	35.7	—	—	30.8	—	—
Effect of bacteremia	Non-bacter- emic	47	6	12.8	32	2	6.2
	Bacteremic	17	3	17.7	16	3	18.8
	% bacteremic	26.6	—	—	33.3	—	—

Among the patients of 40 years or less, the mortality rates were practically the same whether serum or sulfapyridine was used (7 and 6.1%, respectively). In keeping with the expected higher death rates in older patients, the mortality rate for patients over 40 treated with sulfapyridine was 15.8%. Among the serum-treated cases, the death rate in this older age group was 46.2%, or nearly three times as great as for sulfapyridine-treated cases.

When the pneumonia involved only one lobe of the lung, the mortality rates for serum- and sulfapyridine-treated cases were again similar, being 2.2 and 5.5%, respectively. When more than one lobe was involved, the mortality rates for both groups were higher, as was to be expected; but, again, the death rate for serum-treated cases (32%) was much more than that for cases treated with sulfapyridine (18.8%).

When bacteremic patients are considered, the mortality rates were practically the same—17.7% when serum was used, and 18.8% when sulfapyridine was administered. The mortality rate in the 47 non-bacteremic patients treated with serum was 12.8%, as against 6.2% for the 32 patients treated with sulfapyridine.

According to these figures, sulfapyridine seemed to be more effective for elderly patients and for patients with two or more lobes involved, while the two agents seemed to be of equal value in bacteremic cases.

**Mortality Rates. All Types.** The totals at the foot of Table 1 give the results of the treatment of pneumonias caused by all types of pneumococci. When all the cases are considered, 16.7% of those treated with serum died, as compared with 11% of those treated with sulfapyridine. Among the bacteremic cases, the percentages were 23.8 and 20, respectively. The same striking reduction of mortality among cases whose treatment with sulfapyridine was begun during the first 4 days of the disease which was noted for the "lower types" of pneumococcus pneumonias was also found in the entire group, only 3.8% of the patients treated within this period dying, as compared to 13.3% of those treated with serum during the first 4 days.

The severity of the two groups of cases may be compared in Table 3. They are quite similar with regard to the proportion of patients with involvement of two or more lobes (32.3% for serum- and 34.6% for sulfapyridine-treated cases); and also with regard to the percentage of bacteremic patients (23.6% and 20.3% for serum- and sulfapyridine-treated cases, respectively). The groups differ in the relative proportion of patients over 40 years, since there are only 23.8% of elderly patients in the serum-treated group, as compared to 31.6% of patients over 40 years among the sulfapyridine-treated cases.

TABLE 3.—THE EFFECT OF CERTAIN FACTORS UPON MORTALITY RATE IN PNEUMONIAS TREATED WITH SERUM OR SULFAPYRIDINE (ALL TYPES).

		Serum.			Sulfapyridine.		
		No.	Died.	Mortality, %	No.	Died.	Mortality, %
Effect of age	12 to 40	73	5	6.8	83	5	6.0
	Over 40	23	10	47.8	53	10	18.9
	% over 40	23.8	—	—	31.6	—	—
Effect of area of lung involved	1 lobe	65	6	9.7	89	7	7.8
	More than 1 lobe	31	9	30.0	47	8	17.0
	% more than 1 lobe	32.3	—	—	34.6	—	—
Effect of bacteremia	Non-bacter-						
	emic	68	9	13.2	98	8	8.2
	Bacteremic	21	5	23.8	25	5	20.0
	% bacteremic	23.6	—	—	20.3	—	—

**Other Effects.** In addition to observations on the mortality rates, the effect of a therapeutic agent upon the course of pneumonia may be evaluated from other effects. One of these is the incidence of empyema, developing after treatment has been started. Among the 96 serum-treated cases there were 6 cases of empyema, an incidence of 6.1%, while among the 136 patients treated with sulfapyridine empyema developed in 4 (2.9%).

In Table 4, the two therapeutic agents are compared with regard

to their ability to cause a rapid crisis. The patients who experienced a crisis have been classified according to the number of hours from the first administration of sulfapyridine or serum until the temperature reached 100° F. by mouth, and remained below that figure. In the first column are shown the total number of patients recovering after treatment with either agent. In the second column are the cases terminating within 12 hours after treatment was begun; in the third column those terminating within 18 hours, and in the fourth column, 24 hours. The groups in the three latter columns are not mutually exclusive, since cases terminating within 12 hours are also numbered among those terminating in 18 and 24 hours, and cases terminating in 18 hours are also in the 24-hour group. Percentages of patients who had experienced a crisis by the end of each time period, as compared to the total number of survivors, are given.

TABLE 4.—EFFECT OF SERUM OR SULFAPYRIDINE ON THE RAPIDITY OF THE CRISIS IN PNEUMONIA PATIENTS WHO RECOVERED.

Types of pneumococci.	Treated with:	No. of patients recovering.	Patients with crisis.					
			Within 12 hrs. after treatment begun.		Within 18 hrs. after treatment begun.		Within 24 hrs. after treatment begun.	
			No.	%.	No.	%.	No.	%.
Types I, II, V, VII, VIII	{ Serum	60	26	43.3	35	58.3	37	61.7
	{ Sulfapyridine	47	14	29.8	22	46.8	30	63.8
All types	{ Serum	80	30	37.5	42	52.5	44	55.0
	{ Sulfapyridine	121	40	33.1	61	50.4	80	66.1

The most definite results were obtained in the pneumonias caused by Types I, II, V, VII and VIII pneumococci. Among the 60 patients in this group who recovered after serum treatment, a crisis occurred within 12 hours in 43.3%, within 18 hours in 58.3% and within 24 hours in 61.7%. The corresponding figures for sulfapyridine-treated cases were 29.8% for 12 hours, 46.8% for 18 hours and 63.8% for 24 hours. In short, an early crisis occurred more frequently among serum-treated cases, but after 24 hours crisis had occurred as frequently among the sulfapyridine- as among the serum-treated patients.

When pneumonias caused by all types of pneumococci are considered, the same trends are evident, but to a much less degree. In fact, at the end of 24 hours, an even larger proportion of sulfapyridine-treated patients had experienced a crisis (66.1%) than was true of serum-treated patients (55%).

**Discussion.** We are of the opinion that the fairest comparison of the two therapeutic agents should consider only the cases caused by Types I, II, V, VII and VIII pneumococci. There are several reasons for this: First, these types cause a much larger proportion of typical pneumonias than the remaining types of pneumococci.

Cases caused by Types III, IV, VI pneumococci and the types above VIII are more likely to show a spontaneous recovery within the first few days of the disease. Moreover, a larger proportion of cases in the latter group will run their entire course with only a low-grade fever and little evidence of toxicity. If serum had been available for these mild cases, it probably would not have been used, on the theory that they would recover in any event. On the other hand, if they had been scheduled to receive sulfapyridine, there is more likelihood that it would have been given, since the administration of the drug entails less expense and effort. This factor may have influenced the mortality rate in favor of the sulfapyridine-treated group.

Secondly, serum has been shown to be definitely beneficial in pneumonias caused by Types I, II, V, VII and VIII pneumococci, while the evidence in favor of its value in pneumonias caused by the other types is meager.

Thirdly, Types III, IV and VI pneumococci and those above VIII are frequently found in the throats of normal persons and persons suffering from diseases other than pneumonia. Consequently, although we have eliminated all the cases which were obviously virus pneumonias (as described by Reimann<sup>4</sup>), nevertheless, if a few of these cases are still included, they would most likely be found among the pneumonias of this group. On the same basis as mentioned above, they would be more likely to receive sulfapyridine, if they received any therapeutic agent, and this again may have influenced the mortality rate from the drug favorably.

If we compare the 70 "lower-type" pneumonias treated with serum with the 52 "lower-type" cases treated with sulfapyridine, the drug seems to be slightly more effective than serum in lowering the death rate. This superiority is even more evident among the cases treated during the first 4 days of the disease. Sulfapyridine seems to be superior, also, in the treatment of patients over 40 years and patients with two or more lobes involved, while the two agents appear to be equally effective in bacteremic cases.

When the mortality rates for pneumonias of all types are considered, the results were approximately the same as for the "lower-type" pneumonias, except that there appears to be an even greater superiority of sulfapyridine over serum.

Finland and his associates<sup>3</sup> found a 13% mortality rate for patients treated with serum alone, and a 15% death rate for those treated with sulfapyridine alone. In a third group of patients with more severe pneumonias, treated with a combination of the two agents, 26% died. If we add the group treated with both agents to each group treated by a single agent, as has been done in our study, we find that among 247 of Finland's patients who received serum alone or in combination, 17% died. This figure

corresponds closely to the 16.7% mortality rate for our serum-treated cases. Among Finland's 175 cases treated with the drug, alone or in combination, however, there was a mortality rate of 20%, contrasted with 11% among our cases who received the drug. Perhaps our results with sulfapyridine may have been favorably influenced by the use of sodium sulfapyridine, which was given intravenously to some of the patients.<sup>1</sup>

It should be noted that 20 of Finland's patients who were treated with serum also received sulfanilamide. Since there is some evidence that the combination of sulfanilamide and serum may be more effective than serum alone, this may have had a favorable influence upon the mortality rate in Finland's serum-treated group.

Another phase of our study is confirmed by an analysis of Finland's cases. His figures show that there was a higher death rate among the patients over 40 years treated with serum alone (25%) than in similar patients treated with sulfapyridine alone (20%).

Another important item in the comparison of serum and sulfapyridine is the speed of recovery. We have shown that crisis occurs more rapidly in patients receiving serum. This is in agreement with Finland's statement, "With the use of sulfapyridine alone, the patients manifest evidence of illness for a considerably longer period. . . ."

Our results point to the necessity for further study of this problem. We do not believe that any conclusion should be drawn from them for application to the routine treatment of cases of pneumonia, except that both agents are of great value in the treatment of the disease.

**Summary.** 1. Ninety-six cases of pneumococcus pneumonia treated with serum showed a mortality rate of 16.7%, as compared with a rate of 11% for 136 cases treated with sulfapyridine.

2. Mortality rates were essentially the same for bacteremic cases in the two groups, but were definitely lower in the sulfapyridine group for patients over 40 years and for patients with two or more lobes involved.

3. While both serum and sulfapyridine are of great value in the treatment of pneumonia, we do not believe that conclusions may yet be drawn as to their relative value in its routine treatment.

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## CURE OF TYPE XIV PNEUMOCOCCIC MENINGITIS BY SULFAPYRIDINE, CONFIRMED BY AUTOPSY; CASE REPORT.

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SEVERAL reports of cures of pneumococcic meningitis by sulfapyridine have appeared in the literature since the introduction of this drug by Whitby<sup>9a</sup> in May, 1938. Four such cases have been reported in England.<sup>5,6,9b</sup> Barnett *et al.*<sup>1</sup> recently reported results of treatment of 2 cases, of which 1 (Type V pneumococcus) recovered and the other (Type XIV) died 16 hours after administration of the drug was begun. Long<sup>4</sup> cites the results of Hodes, who treated 4 cases with sulfapyridine. Of these 1 recovered and life seemed to be prolonged in 2. Cutts, Gregory and West<sup>2</sup> successfully treated a case of Type XX pneumococcic meningitis with sulfapyridine and serum.

The case here reported is of especial interest in that not only was there clinical evidence of a cure of the meningitis but, due to death from other causes, we were able to confirm the cure at autopsy and to study the residual changes in the meninges. A further interesting point is the observation that sulfapyridine failed to affect the associated and fatal pneumococcic endocarditis.

**Case Report.** K. D., a white female aged 62 was admitted to the medical service of this hospital on Jan. 10, 1939. It was impossible to obtain an accurate history from the patient but it was learned from her family that she had apparently been in good health until 5 days prior to admission, when she had contracted a cold. On the day before admission she seemed no worse, but on the following day did not respond in the usual manner, was rigid and unable to walk. The past history was irrelevant except that the patient had been kept in a nursing home for the past several months because of a mental disturbance (probably senile dementia).

Physical examination on admission showed: temperature 39° C., pulse rate 116 and respiratory rate 23 per minute, blood pressure 150 systolic and 90 diastolic. The patient appeared to be seriously ill but answered questions so far as language difficulties would permit. The pupils were very small, regular, equal, and reacted to light. The nose and ears showed no abnormalities. The pharynx was diffusely red and there was considerable mucus present. There was some resistance of the neck on attempts at passive flexion. The chest was symmetrical and expansion was equal on the two sides. Breath sounds were normal and no râles were heard. The heart was enlarged and there was a harsh, blowing systolic murmur audible at the apex. There was no diastolic murmur. The reflexes were physiologic. Babinski and Brudzinski signs were not present.

Five and one-half hours after admission there was definite nuchal rigidity. Lumbar puncture yielded a cloudy fluid under 11 mm. of mercury pressure containing 3000 cells per c.mm., 80% of which were neutrophils. Direct smear showed many Gram-positive diplococci. By the Neufeld-Sabin method the organisms obtained from culture of the spinal fluid were identified as Type XIV pneumococci. Other laboratory findings were: red blood cells, 5,100,000 per c.mm.; hemoglobin, 15 gm. (Sahli); white blood cells, 25,700 per c.mm. The blood Kline was negative. The urine was not abnormal. Blood culture taken on the day of admission showed no growth.

Oral administration of sulfapyridine\* was begun at 1.30 p.m. on Jan. 11, 13½ hours after admission. The initial dose was 2 gm. Thereafter 1 gm. was given every 4 hours for 5 doses, then 1 gm. every 6 hours until Jan. 21, when it was discontinued. A total of 35 gm. had been given in 10 days.

Within 48 hours of the beginning of this régime the temperature had reached normal (Fig. 1). The spinal fluid cell count had dropped from 3000 to 180 per c.mm. and on the fifth day was at a virtually normal level, which was thereafter maintained. Smears of every sample of spinal fluid taken

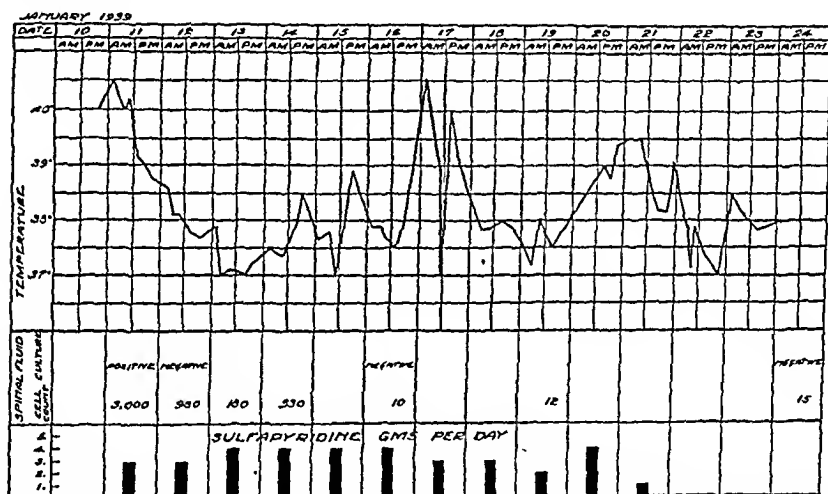


FIG. 1.—Chart showing hospital course, spinal fluid findings and sulfapyridine dosage.

after 24 hours of treatment failed to show organisms. Three of these specimens were cultured and no growth was obtained. Despite these measurable indications of improvement the patient remained seriously ill. Her stupor continued and she ran an irregular febrile course. Râles were heard in the lung bases on the 7th hospital day. On the 9th hospital day the red blood cell count was 3,600,000, the hemoglobin was 12 gm. (Sahli) and the white blood cell count was 21,500. Sulfapyridine was discontinued on the 11th hospital day, because of the suspicion that it was responsible for the fever, but the patient did not improve. An area of discoloration on the medial aspect of the right thigh was noted early in the morning of the 13th hospital day. Her condition became rapidly worse and she died on Jan. 24, the 15th hospital day.

*Autopsy* by one of us (L. L. T.) was begun 4 hours after death. The brain weighed 1255 gm. and was of usual appearance. The leptomeninges were thin and transparent and there was no gross evidence of meningitis. The cerebral arteries were the seat of moderate arteriosclerosis but were patent

\* The sulfapyridine (Dagenan) used in treatment of this case was furnished by Merck & Co., Rahway, N. J.



FIG. 2.—Section of left frontal cortex and leptomeninges showing the typical appearance (low power magnification).





throughout. The venous sinuses presented the usual appearance and contained no thrombi. Sections for microscopic study were taken from many areas of the base and vertex of the brain (Fig. 2). In these the brain parenchyma showed no lesions. There was an increase in the space between the arachnoid and the pia. This space was filled with a coarse network of collagenous fibers, most of which ran parallel to the leptomeninges. In some areas there were large spaces which possibly represented lymphatic spaces but probably were dilated spaces of the subarachnoid. In the collagenous network there were more cells than commonly present. Some of these cells were stellate, with large vesicular nuclei, and the free edges were apparently continuous with the collagenous fibers. In some instances they contained two nuclei. These cells in all ways resembled the undifferentiated mesenchymal cells of Maximov. In addition, there were a few small lymphocytes and large mononuclear cells present. The latter were phagocytic, and often contained vacuoles and finely granular pigment. The walls of the leptomeningeal vessels were unchanged but for thickening of the adventitia due to marked development of a fine reticular and collagenous network. No exudate was seen.

The heart weighed 300 gm. and was not dilated. The epicardium and myocardium appeared as usual. Upon opening the left atrium a large, lobulated mass was seen to extend into the atrium from its attachment near the base of the aortic leaflet of the mitral valve. The mass, though smooth upon the surface, was granular and friable. It measured 2 cm. in length and was firmly attached to an area of the valve leaflet measuring 1 cm. in diameter. This portion of the leaflet felt firm and fibrotic. There was some thickening of the edges of the mitral leaflets and the chordæ tendineæ were thickened and adherent to one another. There was adherence of the right coronary and non-coronary cusps of the aortic valve at the commissure but there was no evidence of recent inflammation. The tricuspid and pulmonic valves were normal in appearance. The mural endocardium was smooth and transparent throughout, showing no lesions. Microscopic section from that portion of the mitral valve to which the vegetation was attached showed many neutrophil cells enmeshed in a network of fibrin. The deeper portions of this zone were infiltrated by large numbers of young fibroblasts and proliferating capillaries. Bacterial stains revealed many Gram-positive diplococci in the vegetation and deep within the zone of inflammation in the valve leaflet. Other significant anatomic findings were: septic embolus in the right common iliac artery with occlusion of the lumen, recent and remote septic infarcts of the spleen and kidneys, and minimal bronchopneumonia of the right lower lobe. Postmortem culture of the heart's blood and culture of the endocardial vegetation yielded Type XIV pneumococci. Bacterial stains of the iliac embolus and of the infarcts of the kidneys revealed many Gram-positive diplococci.

**Comment.** This case demonstrates a cure of Type XIV pneumococcic meningitis. The diagnosis was well established by smears and culture of the spinal fluid as well as by the clinical findings. No organisms were seen in direct smears and all cultures were negative 24 hours after sulfapyridine therapy was instituted. Coinciding with these findings there was a drop in the spinal fluid cell count from 3000 to 15 per c.mm. or below. The spinal fluid remained clear and all clinical signs of meningitis disappeared. Autopsy confirmed the absence of meningitis. The only abnormal finding within the cranial cavity was a slight increase in the cellular stroma and the reticular and collagenous network of the leptomeninges. Similar

changes have been described by Gross, Cooper and Lewis<sup>3</sup> in rats which had recovered from experimental pneumococcic meningitis. They also found lesions of the brain parenchyma in about one-half of their animals, but no such lesions were observed in this case. Weil<sup>8</sup> states that comparable lesions are common in old arteriosclerotic brains, in chronic alcoholism, or in renal disease of long standing. Inasmuch as there was moderate sclerosis of the larger cerebral vessels in this case, it is not possible to state whether the findings were due to the cerebral arteriosclerosis or were a result of the recent inflammatory process, or to a combination of the two factors. The cause of death was a pneumococcic pyemia associated with an acute vegetative endocarditis. There was definite evidence of an old rheumatic aortic and mitral valvulitis, but no activity of this process was demonstrable.

The fibrous tissue reaction in the valve leaflet at the base of the endocardial vegetation demonstrates that the lesion of the mitral valve was of longer standing than the meningitis and that the latter process was probably only a result of the pneumococcemia. Ruegesegger<sup>7</sup> has recently pointed out the high incidence of meningitis as a complication of pneumococcic endocarditis. In his series of 19 cases, 13 (68.4%) terminated in meningitis. Of the remaining 6 cases only 1 failed on postmortem study of the meninges or of the spinal fluid to show evidence of meningitis and in this case the endocarditis was confined to the right side of the heart. Despite the fact that in our case the blood culture taken on admission showed no growth, it is probable that there had been a release of pneumococci into the blood stream, at least intermittently. The fact that the infarcts in the spleen and kidneys were of various ages supports this hypothesis.

That sulfapyridine could bring about cure of the meningitis and at the same time fail seriously to affect the endocardial lesion may be more readily understood in the light of Ruegesegger's investigations.<sup>7</sup> He was able to recover viable organisms from pneumococcic vegetations of the endocardium which had been immersed in formalin for as long as 22 months. The therapeutic effectiveness of any blood-borne agent, chemical or immunologic, must be greatly decreased against any organism so protected in an avascular fibrinous mass. Although the drug failed to destroy the focus of infection, the prompt disappearance of the meningitis is significant evidence that sulfapyridine does affect the course of certain pneumococcic infections.

**Conclusions.** Treatment of a case of Type XIV pneumococcic meningitis associated with pneumococcic endocarditis by the use of sulfapyridine was followed by cure of the meningitis, as judged by clinical criteria as well as by the postmortem examination.

The pneumococcic vegetative endocarditis did not yield to therapy and was responsible for the death of the patient.

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## CHLORIDE EXCRETION IN HYPOPITUITARISM WITH REFERENCE TO ADRENOCORTICAL FUNCTION.\*

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IN the experimental animal, hypophysectomy is followed by atrophy of the adrenal cortex, which can be prevented or corrected by anterior pituitary transplants or by the administration of extracts containing the adrenotropic principle.<sup>8</sup> In hypopituitarism and Simmonds' disease, atrophy of the adrenal cortex is frequently observed<sup>2,4,7</sup> and in a few such patients death has appeared to occur in Addisonian crisis.<sup>6</sup> Asthenia and hypotension are common symptoms, and pigmentation is occasionally seen in hypophyseal cachexia.<sup>5</sup> Low concentrations of whole blood and serum chloride have been observed in hypopituitarism.<sup>9</sup> Anatomical findings would indicate that chronic adrenal insufficiency occurs in pituitary injury<sup>3</sup> and, if so, one might expect to find disturbances of electrolyte balance in pituitary disease. With this in mind, a study of the chloride excretion of a group of patients with hypopituitarism has been made.

The modification of the chloride depletion test recently described by Cutler, Power and Wilder<sup>1</sup> was used. This procedure consists essentially in the administration of a diet low in sodium and chloride and high in potassium, and the administration of measured quantities of fluid and extra potassium as determined by the weight of the patient. The serum chloride is measured at the beginning and at the end of the test period and the concentration of chloride in the urine is measured. The chloride concentration in a 4-hour specimen of urine collected at the beginning of the third day was found by these investigators to be consistently and significantly higher in patients with Addison's disease as compared with a group of control subjects.

Seven patients with demonstrable lesions of the hypophysis were

\* An abstract of this paper was presented at the meeting of the American Society for Clinical Investigation, in Atlantic City, May 1, 1939.

chosen for study. All showed clear evidence of well established hypopituitarism, with complaints of fatigue, weakness, loss of appetite and weight and loss of sexual function. The clinical findings included loss of body, axillary and pubic hair, atrophy of the genitalia, hypotension, decrease in basal metabolic rate and increased glucose tolerance. None of the patients showed evidence of abnormal pigmentation.

During the 52 hours of the test period, the diet described by Cutler, Power and Wilder was given. During the first day of the experimental period free drinking of water was encouraged; on the second day, the fluid intake was adjusted to 40 cc. per kg. and on the third day 20 cc. of fluid per kg. was administered before 11 A.M. On the afternoon of the first day, additional potassium in the form of 42 mg. of potassium citrate per pound of body weight was given. This dose was repeated on the morning of the second day. On the morning of the first day and again on the morning of the third day blood was collected under oil for the determination of serum chloride. On the first and second days the urine was collected from 8 A.M. to 8 A.M.; on the third day, a 4-hour specimen was collected from 8 A.M. to 12 noon. At noon on the third day the test was concluded, the usual hospital diet was resumed and extra amounts of salt were given by mouth for several days.

Non-essential data are omitted from the following case abstracts:

CASE 1.—G.T., a negress, 15 years old, had fallen at the age of 15 months, striking her head. Since that time she had been mentally dull and had suffered from frequent epileptiform seizures. The menses had begun at the age of 12 and had been regular. The general physical examination was essentially negative except for evidences of mental deterioration. The blood pressure was 104 systolic, 58 diastolic. Skin, hair and genitalia were normal. The basal metabolic rate was  $-3\%$ . The fasting blood sugar was 92 mg. %; whole blood chloride, 492 mg. %. Roentgen-rays of the skull showed evidence of an old fracture in the right parietal region.

In the hope of favorably influencing the epilepsy, on October 15, 1935, craniotomy was done and the hypophysis was cauterized, an attempt being made to destroy completely the gland without injuring the neighborhood structures. Following the operation, there was temporary disturbance of water and salt control, and in temperature regulation. During the week after operation, the whole blood chlorides fell to a consistent level of about 420 mg. %. Within 3 weeks the basal metabolic rate had dropped to  $-29\%$ . One year after operation there had been some decrease in the number of epileptiform seizures. The weight had decreased from 56.3 to 46 kg. The temperature was  $35.7^{\circ}\text{C}$ ., the pulse rate 68. The blood pressure was 70 systolic, 50 diastolic. She was dull and apathetic. The skin was dry and cold. Pubic and axillary hair had disappeared. The menses had ceased abruptly at the time of the operation and the external and internal genitalia had become infantile. The fasting blood sugar was 50 mg. %; whole blood chlorides, 456 mg. %; cholesterol, 300 mg. %; uric acid, 3.6 mg. %. The basal metabolic rate was  $-33\%$ . The red blood cells numbered 3,600,000; hemoglobin, 12.7 gm. per 100 cc.

In February, 1939, she was re-admitted to the hospital. At this time there had been little change in her clinical condition. She was mentally

dull and apathetic. The blood pressure was 78 systolic, 60 diastolic. The pubic hair was absent. The uterus was infantile. The basal metabolic rate was  $-47\%$ . The fasting blood sugar was 55 mg. %. During the chloride excretion test there was no significant change in the serum chloride level and the concentration of salt in the urine was found to be within the limits observed in the control subjects (Table 1). She developed no symptoms. About 10 days before the study of chloride excretion was made she had been given 100 units of "Gonadogen" (a gonadotropic preparation of mare serum) without any apparent effect on the sexual organs.

TABLE 1.—CHLORIDES IN HYPOPITUITARISM AND OTHER CONDITIONS.

Patients without evidence of adrenal disease.	Serum chloride—M. Eq. per.L.		Third day, 4 hr. spec. chloride (as NaCl) mg. per 100 cc.	Symptoms.
	First day.	Third day.		
Cutler, Powers and Wilder 28 cases		91.5–103 96.5	28–232 89.4	
R. N., Brucellosis . . .	98	98	150	0
J. B., Brucellosis . . .	100	102	40	0
J. C., Anorexia nervosa . . .		100	141	0
R. P., Coronary occlusion	102	96	244	0
A. N., Pernicious Anemia	101	100	216	0
M. K., Chronic sinusitis .	104	105	100	0
Addison's Disease				
Cutler, Powers and Wilder 7 cases		76.3–94.9 88.2	382–593 489	
Hypopituitarism				
G. T., Hypopituitarism .	96	95	171	0
H. S., Pituitary tumor .	100	92	427	+
J. D., Pituitary tumor .	106	91	494	+
H. B., Pituitary tumor .	103	96	364	0
W. S., Pituitary tumor .	100	90	620	0
T. B., Pituitary tumor .	104	90	503	+
A. B., Pituitary tumor .	94	91	690	+

CASE 2.—H.S., a white male, aged 39, was admitted to the hospital September 3, 1937, with complaint of loss of ambition. He had always been overweight and the beard had always been somewhat scanty, requiring shaving only every 2 or 3 days. For 3 years he had noted increasing lassitude, hypersomnia, loss of libido and potentia. He had lost 20 pounds in weight. Necessity for shaving had been reduced to once a week. There had been no headache or visual symptoms. On examination, the temperature, pulse and respirations were normal. The blood pressure in recumbency was 104 systolic, 60 diastolic; standing, 70 systolic, 50 diastolic. He was somewhat obese, with prominent hips and breasts. The skin was pale, smooth and of fine texture. The beard was sparse and inconspicuous. The pubic hair was thin and of feminine distribution. There was no hair in the axillæ, on the trunk or extremities. The testicles were small and soft; the prostate was so small that it could not be identified with certainty. The red blood cells numbered 3,400,000; hemoglobin, 11.6 gm. per 100 cc.; white blood cells, 6000. The fasting blood sugar was 78 mg. %;  $\frac{1}{2}$  hour after 50 gm. of glucose by mouth, 126; 1 hr. 80, 2 hrs., 102; 3 hrs., 74; 4 hrs., 78; 5 hrs., 73. Blood cholesterol was 232 mg. %; serum chlorides, 626 mg. %; uric acid, 4.7 mg. %. The basal metabolic rate was  $-22\%$ . Roentgen-rays of the skull showed evidence of a large pituitary tumor, with enlargement and erosion of the

sella turcica. The visual fields showed bitemporal upper quadrant defect. On October 15, 1937, craniotomy was done and a cystic pituitary tumor was exposed. Chocolate-colored fluid was aspirated and the capsule of the tumor was removed as far as possible. Histologic section showed a cystic pituitary adenoma of the chromophobe type. The post-operative convalescence was uneventful.

In January, 1939, the patient was re-admitted. There had been little change in his symptoms. The beard had become more sparse and axillary hair had disappeared. Blood pressure was 100 systolic, 60 diastolic. The basal metabolic rate was  $-23\%$ . There had apparently been some decrease in the size of the testicles and further decrease in the size of the prostate which could not be identified. On the third day of the low salt diet the serum chloride decreased to 90 m. eq. and the concentration of salt in the urine was increased (Table 1). During the next day, the patient developed weakness, anorexia, nausea, vomiting, headache and the blood pressure fell to 70 systolic, 40 diastolic. Symptoms were promptly relieved by the intravenous injection of a mixture containing 1000 cc. of water, 10 gm. of sodium chloride, 50 gm. of glucose and 10 cc. of adrenal cortex extract.

CASE 3.—J.D., a 48-year-old man, was admitted to the hospital in December, 1938, with complaints of "tired feeling and lack of pep." These symptoms had been noted for several years but had been more marked during recent months. During the past 5 years sexual libido and potentia had been absent. Between 1924 and 1929 he had had severe intermittent headache which had been unexplained. There had been no recent headache or visual symptoms. Significant physical findings included dry but soft, smooth skin, absence of body hair and scant pubic hair. Visual fields were normal. The blood pressure was 88 systolic, 60 diastolic. The prostate was very small. The basal metabolic rate was  $-14\%$ . The fasting blood sugar was 65 mg.  $\%$ ;  $\frac{1}{2}$  hr. after 50 gm. of glucose by mouth, 101; 1 hr., 105; 2 hrs., 91; 3 hrs., 58; 4 hrs., 71. Roentgen-ray examination of the skull showed a greatly enlarged pituitary fossa measuring 3.5 by 2.3 cm., with destruction of the floor of the sella turcica. On the third day of the chloride excretion test he developed weakness, headache, nausea and vomiting. These symptoms were relieved by the intravenous administration of 1000 cc. of physiological saline solution.

CASE 4.—W. S., a 52-year-old man, was admitted to the hospital in March, 1939, complaining of weakness, dizziness, fatigue and loss of appetite of about 4 months' duration. There had been some diminution of sexual desire. He had lost several pounds in weight. There had been no headache or visual symptoms. The skin was of normal texture. Hair distribution was normal. The visual fields were full. The blood pressure was 114 systolic, 80 diastolic. The testes were small. The prostate was markedly atrophic. Roentgen-rays of the skull showed enlargement of the sella turcica, with depression of the floor and thinning of the dorsum sella. The basal metabolic rate was  $-28\%$ . The fasting blood sugar was 77 mg.  $\%$ ;  $\frac{1}{2}$  hr. after 50 gm. of glucose by mouth, 111; 1 hr., 124; 2 hrs., 110; 3 hrs., 108; 5 hrs., 69. Although the serum chloride fell to 90 m. eq. on the third day and the concentration of salt in the urine was high (Table 1), he developed no symptoms during the chloride excretion test.

CASE 5.—H. B., a 55-year-old man, was admitted to the hospital in 1937, with complaint of headache and failing vision of 1 year's duration. There had been loss of libido since 1934 and body hair had been lost. In December, 1937, a pituitary cyst was evacuated. In February, 1939, he was readmitted. There had been slight improvement in vision but no other change in symptoms. He was chronically ill in appearance. The skin was dry but smooth and of fine texture. The hair was sparse, the eyebrows thin and there was no axillary, body or pubic hair. There was bilateral optic atrophy. Vision

was lost except for the nasal half of the left field. The tongue was large and thick. The blood pressure was 102 systolic, 72 diastolic. The penis was small. Both testicles were small and soft. The prostate could not be identified. The basal metabolic rate was +4%. Blood cholesterol was 227 mg. %. The fasting blood sugar was 74 mg. %;  $\frac{1}{2}$  hr. after 50 gm. of glucose by mouth, 116; 1 hr., 134; 2 hrs., 69; 3 hrs., 78; 5 hrs., 81. Roentgen-ray of the skull showed marked enlargement of the pituitary fossa. The patient developed no symptoms during or after the chloride excretion test.

CASE 6.—T. B., a 49-year-old-man, was admitted to the hospital January 29, 1939. In 1934 he had had craniotomy and partial removal of a chromophobe adenoma of the pituitary because of visual symptoms. After operation vision had improved but during the past year the vision had again been failing and he had been having intermittent headache and occasional nausea and vomiting. The appetite had been poor and he had lost weight. There had been increasing sensitivity to cold and the skin had been dry. Axillary and body hair had disappeared and the pubic hair had become very scant. For several years there had been gradual decrease in sexual function; for 18 months there had been complete loss of sexual libido and potentia. He had noticed that the penis had become small and that the testicles had become small and soft. On examination, he was pale and chronically ill in appearance. He was somewhat overweight. The skin was dry, soft and smooth. The eyebrows and beard were thin. There was no axillary or body hair. The pubic hair was very sparse. He was mentally dull and irritable. The right pupil did not react to light. There was bilateral optic atrophy, more marked on the right. Vision was lost except for the nasal half of the left field. The blood pressure was 90 systolic, 60 diastolic in recumbency; 72 systolic, 58 diastolic sitting. The testes were small and soft, each about the size of a robin's egg. The prostate was very small, flat and vaguely outlined. The basal metabolic rate was - 37%. The blood cholesterol was 480 mg. %. The fasting blood sugar was 86 mg. %;  $\frac{1}{2}$  hr. after 50 gm. of glucose by mouth, 73; 1 hr., 75; 2 hrs., 64; 5 hrs., 95. Roentgen-rays of the skull showed marked enlargement of the pituitary fossa, with thinning and depression of the floor, thinning of the dorsum sella to paper thickness and erosion of the posterior clinoids. On the third day of the chloride excretion test he developed headache, weakness, irritability, nausea and vomiting. These were relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract. During the next few days he was given extra salt by mouth (Chart 1). The chloride excretion test was then repeated with the daily administration of 5 cc. of adrenal cortex extract intramuscularly. The changes in the serum chloride and urine chloride concentration were modified and he failed to develop symptoms.

CASE 7.—A. B., a 57-year-old man was admitted to the hospital in January, 1938, with history of 2 years' duration of fatigue, weakness and weight loss. He had lost 60 pounds during the first 8 months of the illness and had developed marked anorexia, loss of hair, dryness of the skin, loss of sexual desire and increased sensitivity to cold. Between June, 1936, and September, 1937, he took injections of various anterior pituitary extracts; during this time his appetite improved and he gained about 45 pounds in weight. The other symptoms remained about the same. Between September, 1937, and January, 1938, he had been without treatment, had lost 20 pounds and complained of increased fatigue, weakness and anorexia. On examination, he was poorly nourished and appeared chronically ill. The skin was dry, smooth and of fine texture. The hair was thin and sparse. The blood pressure was 85 systolic, 58 diastolic. The weight was 70.4 kg. Roentgen-ray of the skull showed marked enlargement of the pituitary fossa, with thinning of the floor and of the dorsum sella. The basal metabolic rate was -30%. Blood cholesterol was 250 mg. %. The fasting blood sugar



was 71 mg. %;  $\frac{1}{2}$  hr. after 50 gm. of glucose by mouth, 180; 1 hr., 125; 2 hrs., 61; 3 hrs., 62.

In January, 1939, he was readmitted. During the past year he had been given intramuscular injections of an anterior pituitary extract 3 times weekly and had taken 2 grains of desiccated thyroid daily. In spite of such treatment he had lost 40 pounds in weight and had developed extreme anorexia, marked weakness and fatigue. There was absence of sexual desire and potency. He was abnormally sensitive to cold and had ceased to perspire. He had noted decrease in size of testes and penis. On examination, he was apathetic, depressed and irritable. He appeared emaciated and chronically ill. Weight was 52 kg. The skin was dry, and smooth. The beard was sparse. There was no axillary or body hair. There were a few fine, long hairs on the arms. The pubic hair was scant and of feminine

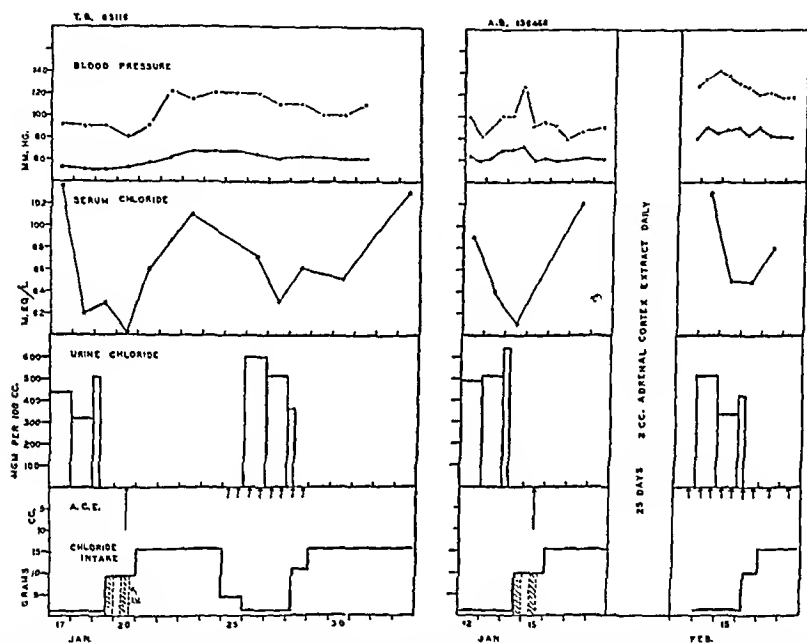


CHART 1.—Observations of blood pressure, serum chloride and urine chloride concentration in 2 patients with hypopituitarism before and after the administration of sodium chloride and adrenal cortex extract (A. C. E.)

distribution. The blood pressure was 108 systolic, 60 diastolic in recumbency; 92 systolic, 64 diastolic standing. The penis was small. The testes were atrophic, measuring about 2 by 4 cm. The prostate was very small and flat. The basal metabolic rate was -42%. The fasting blood sugar was 62 mg. %;  $\frac{1}{2}$  hr., after 50 gm. of glucose by mouth, 159; 1 hr., 102; 2 hrs., 50; 3 hrs., 54. On the third day of the chloride excretion test he became nauseated, vomited 3 times and was weak, apprehensive and exhausted. These symptoms disappeared after the intravenous administration of fluid, salt, glucose and adrenal cortex extract.

During the following 25 days he was given 2 cc. of adrenal cortex extract and took 10 gm. of extra salt daily. He returned on February 14th and reported increased appetite, increase in strength and an improved mental outlook. The physical findings were essentially as before except that the blood pressure was 130 systolic, 84 diastolic. The basal metabolic rate had

increased to  $-11\%$  (2 determinations). The weight was 53 kg. The second chloride excretion test showed modifications in the serum and urine chloride changes (Chart 1). This time he developed no symptoms.

He continued to take 1 cc. of adrenal cortex extract intramuscularly and 10 gm. of extra salt by mouth daily. On April 11, 1939, he weighed 66 kg., having gained 31 pounds. He had developed a ravenous appetite, had improved markedly in strength and endurance and was enthusiastic, cheerful and encouraged in contrast to the previous apathy and depression. The systolic blood pressure had increased to between 140 and 160, the diastolic to between 80 and 88.

**Discussion.** Table I shows a summary of the observations of serum chloride and urine chloride concentration in the patients with hypopituitarism and in a group of control subjects without evidence of endocrine disease. In the control group, there was no significant change in the serum chloride levels and the excretion of salt in the 4-hour specimens collected at the beginning of the third day was in the range observed by Cutler, Power and Wilder<sup>1</sup> in a larger group of similar subjects. The first patient with hypopituitarism, in whom the hypophysis had been removed some years before, showed a normal response to the test. It is possible that the results may have been modified by the recent administration of Gonadogen. Each of the other 6 patients with hypopituitarism showed significant decreases in serum chloride during the period of chloride depletion and a high concentration of salt in the 4-hour third day urine specimen in the range found by Cutler, Power and Wilder to be characteristic of adrenocortical insufficiency. Four of these 6 patients developed symptoms suggesting those of the Addisonian crisis, associated with decrease in the serum chloride level. These symptoms were promptly relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract. In 4 patients in whom the serum sodium was determined it was found to be decreased on the third day of salt depletion. No significant changes in the non-protein nitrogen or the carbon dioxide combining power of the blood were observed.

In 2 of the patients who had developed symptoms the test was repeated after the administration of salt and adrenal cortex extract. During the first period of salt depletion 1 patient (T. B.) had developed symptoms on the third day which were relieved by the administration of salt and adrenal cortex extract. After several days of high sodium chloride intake, the test was repeated with the daily administration of 5 cc. of adrenal cortex extract. The results were modified in that the serum chloride level fell to 95 rather than to 90 m. eq. and the concentration of salt was lower than in the first experiment, but still in the abnormal range. This time he developed no symptoms. The second patient (A. B.) developed symptoms on the third day of the test with a serum chloride level of 91 m. eq. He left the hospital and for 25 days took extra salt and adrenal cortex extract daily. Repetition of the test resulted in a modifica-

tion of the serum and urine chloride changes (Chart 1) and he developed no symptoms. The continued administration of salt and adrenal cortex extract resulted in striking clinical improvement and gain in weight. The doses of adrenal cortex extract which were used were so small that one suspects that the modifications in chloride excretion and the striking clinical improvement in the second patient may have been due to the extra salt intake as much as to any specific effect of adrenocortical substance.

These observations appear to confirm the impression that limitation of adrenal function occurs in hypopituitarism and suggest that this factor should be taken into consideration in the treatment of such patients and in the differential diagnosis of hypopituitarism and Simmonds' disease. There may, however, be other factors in pituitary disease which conceivably might influence the electrolyte balance. For example, Thorn and Engle<sup>10</sup> have shown that the sex hormones, progesterone, testosterone and the oestrogens, as well as the adrenocortical principle may cause retention of electrolytes in the normal and adrenalectomized animal and in patients with Addison's disease. Although experimentally the sex hormones are effective only in relatively large doses, the question is raised as to whether the changes observed in this group of patients may have been associated with secondary gonadal as well as adrenal insufficiency. In none of the patients with hypopituitarism was there evidence of pulmonary or renal disease or of involvement of the hypothalamus or posterior pituitary which might have influenced salt excretion.

**Summary.** Six of 7 patients with clinical hypopituitarism, when studied under standard conditions of salt depletion, showed increased concentrations of chloride in the urine similar to that which has been found to be characteristic of adrenocortical insufficiency.

Four of the 6 patients developed symptoms suggesting those of Addisonian crisis. These symptoms were promptly relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract.

In 2 patients symptoms failed to occur and chloride excretion was favorably modified after the administration of sodium chloride and adrenal cortex extract. One patient experienced striking clinical improvement during the administration of sodium chloride and adrenal cortex extract.

These observations are interpreted as confirmatory evidence of the occurrence of chronic adrenocortical insufficiency in clinical hypopituitarism, presumably secondary to withdrawal of the adrenotropic anterior pituitary principle.

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The adrenal cortex extract used in this study was provided by The Upjohn Company.

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## THE AMOUNT OF LYMPHOID TISSUE OF THE HUMAN APPENDIX AND ITS WEIGHT AT DIFFERENT AGE PERIODS.

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THIS presentation is part of a general study of the morphologic changes of human lymphatic tissue at different ages, an investigation stimulated by a consideration of the problems in ageing, in the book of that name edited by E. V. Cowdry.<sup>6</sup> Though the lymphatic tissue taken as a unit is probably one of the largest organs of the body, being said to be even larger than the liver, its widely scattered distribution and rapid response to environmental change make quantitative studies difficult. For instance, while it is accepted that the various lymphatic tissues of the human body begin to retrogress at different periods in the life cycle, actual figures on the subject are extremely meager. As an example of retrogression differences, the thymus, one of the components of this complicated system, has already begun its involutionary changes before sexual maturity and while the lymphatic tissue elsewhere is still developing toward a maximum. Having completed a study in the spleen, which analyzed the weights of 4000 supposedly normal spleens and the amount of splenic lymphatic tissue in 300 violent deaths at different ages,<sup>5</sup> we now offer the results of a similar study on the appendix. Difficulties in obtaining "normal" material and the time and the labor involved in securing the necessary data are apparently the main reason that these problems have not already been adequately studied.

Muthmann's study of the appendix<sup>7</sup> led him to the view that regression starts early in childhood, while Berry and Lack<sup>3</sup> and

\* Part II of thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for graduate work in Pathology for the degree of Doctor of Medical Science (D.Sc. (Med.)).

Corner<sup>4</sup> found that it began later in life. Stefancelli<sup>8</sup> claimed that normally no lymphatic follicles could be found in the appendix after the age of 75, while the latest study of Bernardo-Comel<sup>12</sup> found, as we have also (Chart 1), that they persisted throughout life. Because of such sparse and yet divergent experiences, and the differences in methods and material, much of it being from diseased organs or from autopsies after death from disease, a more rigidly controlled investigation seemed desirable.

**Methods.** Human appendices from 300 cases of sudden, violent deaths, excluding individuals who were found either from the history or postmortem examination to have any recognizable disease or to have survived more than 10 hours after the violence, were studied by the methods outlined in the spleen study. In this material, chief causes of death were automobile accidents and gun-shot wounds (excluding those of the abdomen); except for a few cases of carbon monoxide poisoning, all poison cases were excluded. Each appendix was placed in formalin with a portion of the cecum and the mesoappendix attached, ensuring that the whole appendix had been received. The cecum and mesoappendix were removed before the appendix was weighed. This affords weight comparisons between the appendices studied here, but not between these and unfixed appendices, as organ weights change considerably during and after formalin fixation. Blocks were taken from each appendix at three different levels (proximal, middle and distal). All of these blocks included the lumen. The blocks were embedded in paraffin, sections cut at approximately  $6\mu$  in thickness, stained with Harris' hematoxylin and eosin, and low power fields ( $8.6\times$ ) projected for outlining, as in the spleen study. Three outlines were traced: the walls of the appendices, their included lymphatic follicles, and the "pale centers," if present; the areas of the total cross section, the lymphatic follicles, and the pale centers were afterwards measured with the planimeter. Further details of the method can be found in the spleen article.

The percentage of lymphatic tissue as a whole in the section is termed the "gross" percentage and that from which the "pale centers" had been deducted, the "net." The weight of the lymphatic tissue was calculated by multiplying the weight of the organ by the percentage of lymphatic tissue found. The marginal zone (*Aussenrandzone*) encountered in the splenic series was not met with in this series, and the traced areas were found to be sharply defined. Beyond the follicles the mucosal zone contained only a few isolated lymphocytes, so that the estimation of the follicular areas as representing the total lymphatic tissue was less open to subjective error than in the case of the spleen study. For comparison, in 10 cases sections were also made longitudinally, or parallel to the long axis of the appendix, as a control for variations not covered by this procedure, and in 6 cases cross sections were made at various levels between the proximal and distal sections. We found that the percentages obtained in these controls were not significantly different from those found in the three standard sections described above. The larger total amount of lymphatic tissue obtainable in the longitudinal sections would have constituted preferable material, had it not been for the unavoidable damage to the mucosa while spreading the fixed

specimen; thus, of course, vitiating the percentages obtained. In about 90% of the specimens received, the lumen contained yellowish fecal material; most of these appendices had a smaller external circumference at the middle portion than at either the proximal or the distal ends.

Each specimen was studied microscopically before projection for signs of acute or chronic inflammation, fibrosis, and other definite lesions. Where any such lesions were present, the material was discarded (more than 70 appendices beyond the 300 analyzed). Those that had many "pale centers" were scrutinized for disease with

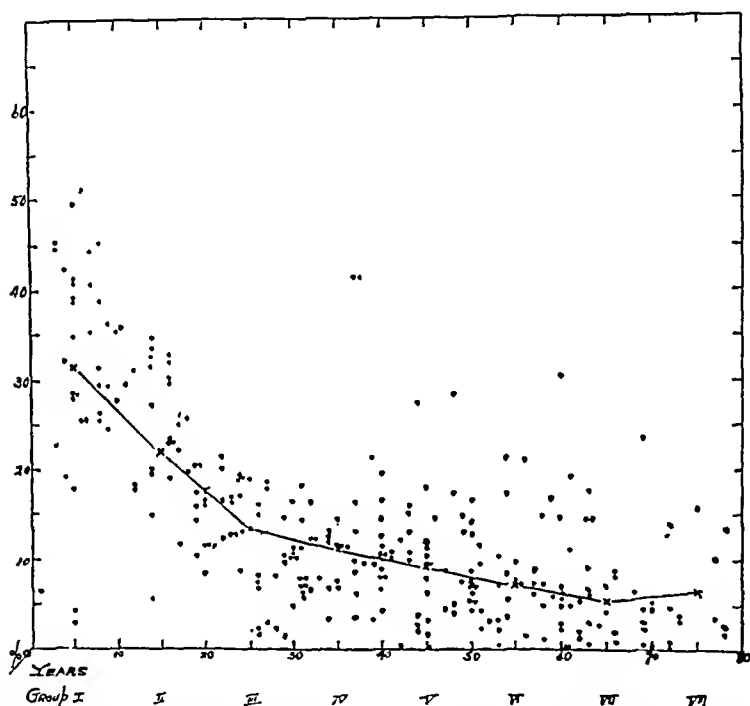


CHART 1.—"Gross" percentage of lymphatic tissue of the human appendix at different ages in 300 cases of violent deaths. Dots indicate individual percentages, the curve indicates the mean for each decade.

special care, though it was eventually found that they exhibited lesions in no greater numbers than did the rest of the material.

**Results.** Fortunately the material was distributed fairly evenly among the different age groups, with the exception of cases in the first year of life and those over 80. Except for these and the 71-80 age group (Group VIII), in which the cases numbered 14, all groups contained not less than 30 cases each.

The "gross" percentage of lymphatic tissue, as shown by Charts 1 and 2, starts at a maximum in the first decade. The single case less than one year old, showed a small percentage of lymphatic tissue,

just as in the splenic series at that age; it is probable that a larger number of cases at this age would show a low average percentage in the first year of life. The lymphatic percentage drops sharply in the second and third groups, and then very slowly though steadily until the seventh group, where a small elevation of the curve is noticed. A difference between the "gross" and "net" percentages of lymphatic tissue (*i. e.*, due to existence of "pale centers"), and also between the "gross" and "net" weights was readily observable only in the first two groups (1-10 and 11-20 years).

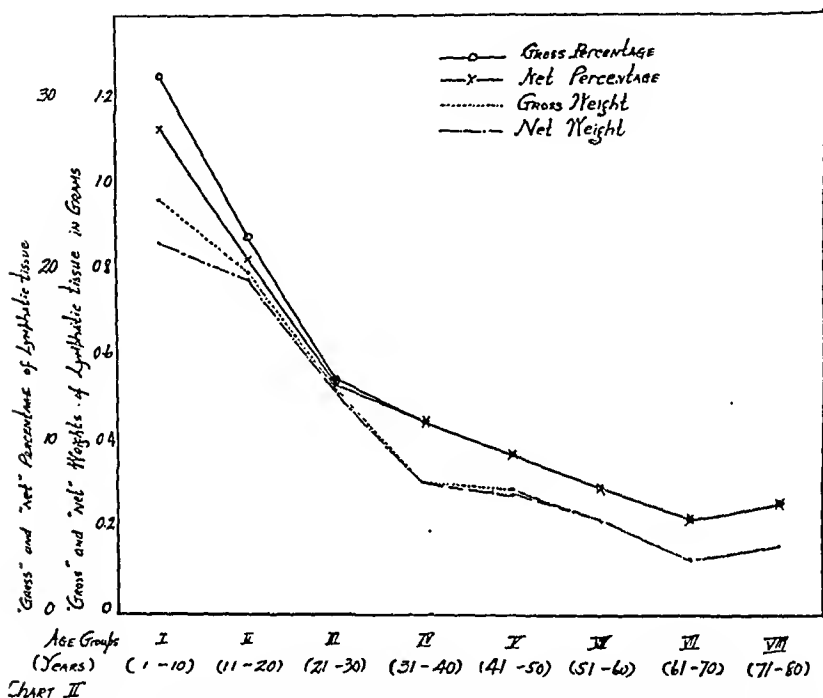


CHART 2.—"Gross" and "net" percentages and calculated weights of lymphatic tissue in the appendix at different ages.

It is also of interest to note that a number of appendices over 40 years showed considerable fatty deposits in the submucosa. These we included in our series, though their presence, of course, influenced both the mean percentages and absolute weights. However, this may be a phenomenon of the actual ageing process of the appendix and thus of its included lymphatic tissue.

About 3% of our specimens showed more or less obliteration of the lumen. These 9 appendices all fell in the last three age groups. In spite of the obliterations, characterized by thin strands of fibrous tissue with included fatty deposits, no other abnormalities could be found, though they always showed a minimum amount of lymphatic tissue.

TABLE 1.—LYMPHATIC TISSUE OF APPENDIX AT DIFFERENT AGES IN 300 CASES OF VIOLENT DEATH.

Group.	No.	Absolute weight.		Percentage.		
		Mean.*	Standard error of mean.	No.	Mean.	Standard error of mean.
O (0-1 yr.)	1	0.21		1	12.1	
I (1-10 yrs.)						
"Gross"	36	0.97	0.05	36	31.4	1.9
"Net"	36	0.87	0.04	36	28.4	1.65
II (11-20 yrs.)						
"Gross"	39	0.80	0.075	39	22.1	1.2
"Net"	39	0.79	0.075	39	20.9	1.2
III (21-30 yrs.)						
"Gross"	40	0.53	0.070	40	13.7	1.0
"Net"	40	0.52	0.070	40	13.5	1.0
IV (31-40 yrs.)						
"Gross"	46	0.31	0.03	46	11.3	0.8
"Net"	46	0.31	0.03	46	11.3	0.8
V (41-50 yrs.)						
"Gross"	45	0.29	0.03	48	9.4	0.8
"Net"	45	0.28	0.025	48	9.3	0.7
VI (51-60 yrs.)						
"Gross"	42	0.22	0.03	42	7.4	1.0
"Net"	42	0.22	0.03	42	7.4	1.0
VII (61-70 yrs.)						
"Gross"	32	0.13	0.02	32	5.5	0.85
"Net"	32	0.13	0.02	30	5.5	0.85
VIII (71-80 yrs.)						
"Gross"	14	0.16	0.04	14	6.5	1.35
"Net"	14	0.16	0.04	14	6.5	1.35
IX (81-90 yrs.)						
"Gross"	2	0.48		2	21.3	

\* The mean absolute weight in each group was obtained from absolute weights calculated for each individual, rather than by multiplying the group means of appendix weights by the lymphatic percentages.

The single appendix from an infant less than one year old had definitely less lymphatic tissue than the other appendices of the first decade. The two specimens from persons over 80 happened to have more lymphatic tissue than those of the previous decade (see statistical analysis).

Analysis according to sex revealed that the percentage and absolute weight, both the "gross" and "net," were significantly lower in the female than in the male (Table 2).

The weight of the appendix (Table 3, Chart 3) reached its maximum in the second age group (11-20 years), and thereafter receded gradually and steadily. Tables 1 and 3 show that the calculated gross lymphatic weight dropped 17% from Group I to Group II, while the total weight of the appendix showed a rise of 45%; from Group II to Group III the lymphatic tissue revealed a drop of 34% while the appendiceal weight attained a drop of only 13%; and from Group III to Group IV, a 41% drop was found in the lymphatic weight, but only a 10% drop in the weight of the appendix. From Group V on, the loss in both the lymphatic and appendiceal weights runs practically parallel.



TABLE 2.—“GROSS” AND “NET” LYMPHATIC WEIGHTS AND PERCENTAGES ANALYZED ACCORDING TO AGE AND SEX.

Group.	No. of cases.			Lymphatic weights.		Lymphatic percentages.	
	Male.	Female.		Male.	Female.	Male.	Female.
I	26	10	“Gross”	1.01	0.88	32.9	27.3
			“Net”	0.91	0.80	30.6	21.8
II	32	7	“Gross”	0.86	0.57	22.6	20.3
			“Net”	0.84	0.55	21.4	19.5
III	31	9	“Gross”	0.54	0.49	13.7	12.7
			“Net”	0.53	0.49	13.5	12.5
IV	39	7	“Gross”	0.33	0.23	11.5	10.3
			“Net”	0.33	0.23	11.5	10.3
V	42	6	“Gross”	0.30	0.24	9.2	11.2
			“Net”	0.29	0.23	9.1	11.1
VI	34	8	“Gross”	0.23	0.27	7.1	8.6
			“Net”	0.23	0.27	7.1	8.6
VII	26	6	“Gross”	0.14	0.10	5.6	5.2
			“Net”	0.14	0.10	5.6	5.2
VIII	13	1	“Gross”	0.17	0.05	6.8	3.4

**Statistical Analysis.** The peak of the curves of both percentage and calculated absolute weight of the lymphatic tissue is in the 1-10 year old group (Table 1, Chart 2).

In the curves of the absolute lymphatic weights, both “gross” and “net,” in Groups I to IV (Table 1, Chart 2) the means are both steadily and significantly different from each other (*i. e.*, in each case the difference of the means is greater than twice the standard error of the mean).

The curve of “gross” lymphatic weights for Groups I to IV inclusive is sharply down grade, with a regression coefficient of  $-0.23$ . From Group IV to Group VIII, the slope is more gradually downhill—but definitely so—with a regression coefficient of  $-0.175$  and a standard error of the regression coefficient of  $0.02$ . As the value of  $-0.075$  is about four times  $0.02$ , the slope is definitely downgrade, the regression coefficient of a horizontal line being  $0$  (Table 1).

The values for the 2 cases in Group IX (not on chart) are much greater and about at the limit of significant difference from those of Group VIII. However, this cannot be taken as indicating a tendency of lymphatic tissue to increase at this age period, unless confirmed by a much larger number of cases. The rise in Group VIII is not statistically significant. The lessened downward tendency in Group V is of interest as occurring at about the same age as a more definite hump in the curve of splenic lymphatic tissue.

TABLE 3.—WEIGHTS OF APPENDICES AT DIFFERENT AGES.

Group.	Gm. (fixed in formalin).
I	2.57
II	3.74
III	3.23
IV	2.89
V	2.73
VI	2.54
VII	2.05
VIII	2.04

The curve of the "gross" percentages of lymphatic tissue is much the same as that of the absolute weights, but the sharper decline stops one group earlier, at Group III rather than Group IV. Therefore, the regression coefficient of the first three groups is  $-8.8$ ; of Groups III-VIII is  $-1.45$  with a standard error of the coefficient of  $0.28$ .

The curves of the "net" percentages (*i. e.*, excluding the "pale centers") are much the same as those of the "gross" percentages. The only difference is a considerably and significantly lower value in Group I, and a smaller difference in Group II.

**Discussion.** In the present series, except for the cases in the first few months of life and those over 70 years of age, there are about the same number of cases in each age group, and enough for adequate statistical study. We recognize a handicap that seems insurmountable in such a study, namely that in an uncertain number of cases both total weight and percentage of lymphatic tissue may have been permanently modified by the effects of previous inflammation without leaving telltale signs. The results have proven, however, to be more consistent than in the spleen study, with a corresponding increase in significance. There is apparently a steady decrease in the lymphatic tissue of the appendix throughout life, after the maximum has been reached in the first age group. As in the case of the spleen material, the lymphatic tissue is apparently small in the first few months of life, though we have not had adequate material to be certain on this point.

Subtraction of the "net" from the "gross" figures on the lymphatic tissue gives an estimate of the amount of space occupied by the "pale centers." Only in the first decade (to a lesser extent in the second decade) do these play any noticeable rôle. The interpretation of these observations depends on what these "pale centers" are taken to represent. As indicated in our previous treatment of this subject, we believe that they may under different circumstances either serve as true lymphoblastic tissue, so-called "germinal centers," or more frequently as "reaction centers" made up of elements of the reticulo-endothelial system. From this point of view, the "pale centers" in the first age group are taken to be lymphoblastic, at a time when the young lymphatic tissue is actively hyperplastic. The absence of the "pale centers" in later life (*i. e.*, when they are regarded as usually being "reaction centers,") is taken as a further indication of the normal quality of the material (*i. e.*, absence of inflammatory processes in the body at the time of the violent death).

The gross weight of the 300 appendices also showed a steady decline after an initial increase from the first to the second decade of life. In the "spot" chart of individual appendix weights (Chart 3) it will be seen that there is a marked increase in appendiceal weight with the fourteenth year, an indication in accord with the observations of other authors, and also with our spleen material (see the "spot"

chart of that study), that human lymphatic organs tend to increase markedly in weight at the time of puberty. Analysis of the decline in total appendix weight after puberty shows that it is not as marked as that of the lymphatic tissue within the appendix in the same age periods.

The maximum weight of the organ and of its lymphatic tissue content (in the first decade of life, when taken by decades) appears to be reached earlier than in the other lymphatic tissues of the body, excepting the thymus. This, however, is not altogether incompatible with the generalization that infections tend to be most prevalent

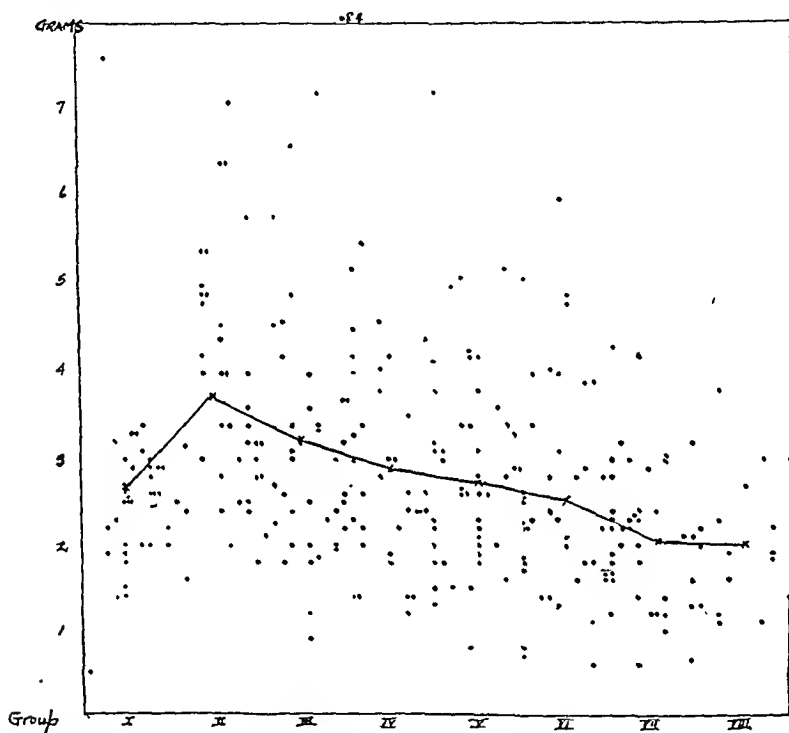


CHART 3.—The weights of the formalin-fixed appendices at different ages in the 300 cases. Dots indicate individual weights, the curve indicates the mean for each decade.

at ages when lymphatic tissue is abundant. Appendicitis is rare in infancy when appendiceal lymphatic tissue appears to be scanty; it is not infrequent in the prepubertal period, and, according to Ashhurst<sup>1</sup>, is commonest from 10 to 30 years. When the other factors that contribute to appendicitis are taken into account, this will be seen to constitute a fairly good correlation. Its significance is quite another matter; it is difficult to understand why the individual should be most susceptible at a time when a system that is accepted as being a defense mechanism is at or near its maximum. This discrepancy is even more difficult to understand in the case of the appendix than in that of the tonsils, where the persistence of foci

of infection and distortion from previous attacks undoubtedly play a greater rôle in frequent attacks than they do in the appendix.

Analyzed according to sex, the calculated weight of the lymphatic tissue in the appendix is significantly less in females, though this observation is weakened by the smaller number (about 25%) of females in the series and by the absence of data on the total body weights. Up to the forty-first year, the lymphatic percentages are also less in the female than in the male. Analyzed according to sex, the gross weights of our 4000 spleens are in accord with the appendix figures, in that the female spleens are lighter than the male spleens, and the difference in spleen weights is greater than that of the total body weights of the two sexes. The reason for these differences is not apparent.

We were especially interested in comparing the amount of lymphatic tissue in the appendix in the later decades of life. In our spleen studies, we found suggestive increases (or a tendency to level off the falling curve) in the age periods between 50 and 65 years. The present study, however, fails to show such a change (the slight leveling from 41 to 50 years being insignificant); and thus gives no support to the suggestion raised by our spleen material and occasionally found in the literature, to the effect that there is a tendency for the lymphatic tissue to show a secondary increase in later life.

**Summary and Conclusions.** 1. The amount of lymphatic tissue in the human appendix has been studied in 300 persons dying violent deaths, and analyzed according to eight age groups and to sex.

2. The percentage of the lymphatic tissue and its calculated weight were found to be greatest in the first age group (1 to 10 years) and to diminish fairly steadily throughout life. The later secondary rise found in our spleen material was not observed.

3. The appendix attains its maximum weight in the second decade, about the age of puberty, and then decreases in weight throughout life, but less markedly than does its lymphatic tissue.

4. The female appendix apparently contains less lymphatic tissue than the male throughout life.

We are extremely grateful to the following medical examiners and coroner's physicians for their generous help in furnishing material: Dr. Helpert, of the Manhattan Medical Examiner's office; Dr. Werne, of the Jamaica, L. I., office; Dr. Leary, of Boston; Drs. Wadworth, Crane, and the other coroner's physicians of Philadelphia. We also wish to thank Miss Isabel Hassler and Miss Ruth King for their technical help, and Mr. M. S. Abel for statistical assistance.

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## FURTHER STUDIES OF THE INTRACUTANEOUS METHOD OF TYPHOID VACCINATION.\*

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IN 1932, Yagle, Rogers and the author<sup>10</sup> reported the results of a comparative study of the antibody response after the administration of a mixed typhoid vaccine by the intracutaneous, subcutaneous, intramuscular, intravenous and oral routes. This study indicated that insofar as agglutinins and complement-fixing antibodies were concerned the response was uniformly better and more persistent after local injection. This was particularly true of the intracutaneous route, even though the total dose by this method was only one-fifth of that given subcutaneously or intramuscularly. These observations helped to substantiate the fact as indicated by other experiments and by a review of the literature which the author reported in 1931,<sup>9a</sup> that the skin was an extremely important immunologic organ and that it participates very actively in antibody production. This conception of the skin as an active agent in immune antibody production as well as our demonstration of the marked antibody production after intracutaneous injection of typhoid vaccine suggested the utilization of this route of administration in routine typhoid immunization. A study of the response of more than 100 individuals who were given four doses (0.05, 0.1, 0.15 and 0.2 cc.) of typhoid vaccine intracutaneously at weekly intervals indicated that this method of vaccination gave a satisfactory immunologic response; also that the injections were accompanied by considerably less local reaction and by almost complete elimination of those annoying constitutional symptoms that follow other methods of administration. Because of these advantages, it was suggested that the intracutaneous method be used in typhoid immunization instead of the subcutaneous or intramuscular routes.<sup>9b</sup>

Subsequent to the publication of these studies, additional verification of the efficacy of the intracutaneous route of immunization was furnished by its employment for purposes of active immunization in the lower animal as, for example, with pneumococcus vaccine. Likewise, Kern and his co-workers, encouraged by our results with typhoid vaccine, successfully utilized the intracutaneous method in active immunization against diphtheria with diphtheria toxoid<sup>5</sup> and against scarlet fever with scarlet fever streptococcus toxin.<sup>6</sup> They

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were able to show that positive reactors could be rendered Schick- and Dick-negative by the intracutaneous administration of much smaller doses; furthermore, there occurred a marked reduction or almost complete elimination of those discomforting and at times severe local and constitutional reactions that were so frequent, especially in adults.

Prior to the time of our original publication, most of the immunologic studies in typhoid infection or after typhoid vaccination usually were concerned with the agglutinin response as a whole without attempting to differentiate the type. In recent years, more attention has been given to their differentiation as originally proposed by Felix,<sup>3</sup> into a species-specific somatic or "O" agglutinin and a type-specific flagellar or "H" agglutinin. Felix and others<sup>1,4</sup> have shown that the O agglutinin appears earlier and in higher titer in frank typhoid infection than the flagellar or H agglutinin and seems to indicate a more favorable prognosis. The H agglutinin, on the other hand, was produced in higher titer than the O antibody in vaccinated individuals. Contrary to the original conclusion of Felix, that O agglutinins do not appear in vaccinated individuals, observations, particularly by Dulaney and his co-workers,<sup>2</sup> and by Perry,<sup>7</sup> have shown that these antibodies do appear in vaccinated individuals. Perry's report is of further interest to the present study because he showed that the H and O agglutinins appeared in equally high titers and that these titers were the same in the group of individuals given the vaccine intracutaneously in doses of 0.05, 0.1 and 0.1 cc. as in those given the vaccine subcutaneously in doses of 0.5, 0.8 and 1 cc. at weekly intervals; also, one dose of vaccine (either 0.1 cc. intracutaneously or 1 cc. subcutaneously) given to previously vaccinated individuals was sufficient to increase the titer of both H and O agglutinins to a point beyond that of the non-vaccinated group; also, that these persisted in the blood for as long as a year in more of these individuals than in the non-vaccinated group. Furthermore, Perry confirmed my original observation that the intracutaneous injection of vaccine rarely resulted in a systemic reaction, which was in contrast to that of the subcutaneously injected individuals.

One of the difficulties in estimating the effectiveness of typhoid immunization from a laboratory standpoint is the necessity for depending entirely upon antibody response in vaccinated individuals. This is unsatisfactory since the presence of agglutinins which are taken as the usual indicator does not persist in adequate amount for more than 3 to 6 months and in most instances are absent from the blood within a year. This does not mean, of course, that such an individual is not immune. Experience with vaccinated individuals in epidemics and especially in the army has indicated that actively acquired immunity of this type may persist for a much longer time. It is neither feasible nor desirable, of course,

to test the efficacy of vaccination in civilian life by direct exposure to infection: for this reason, any test which will shed some light on the protective power of the blood of such individuals would be more helpful. This has been furnished to some extent by the use of the mouse-protection test, employed originally for other organisms, but adapted for the typhoid bacilli by Siler.<sup>8</sup> In this test the serum of the patient is injected intraperitoneally into mice followed in  $\frac{1}{2}$  hour by measured amounts of the causative organisms, using as controls mice which received only the organisms. If the serum prevents death of the mice from infection in certain dosage in comparison to the controls, it is taken as an indication that protective antibodies are present.

In spite of the seemingly obvious advantages of the intracutaneous method of typhoid immunization as well as the definite evidence of satisfactory immunologic response, this method has not as yet been generally adopted. Before making further recommendations, it was decided to carry out studies designed to re-check our original observations as to the immunologic response to intracutaneous typhoid vaccination with additional observations as to the effect not only upon the H agglutinins but also upon the O agglutinins and upon the bacteriolytic power as measured by mouse-protection tests. Accordingly, the following studies were carried out:

**Procedure.** 1. A group of 45 individuals who had never been immunized previously against typhoid were injected subcutaneously at weekly intervals with 0.5 cc., 1 cc., and 1 cc., respectively, of typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cubic centimeter. A second group of 56 individuals who likewise had never been immunized previously against typhoid were injected intracutaneously at weekly intervals with 0.1 cc., 0.15 cc. and 0.2 cc. of the same vaccine. Record was made of any marked local reaction or any constitutional symptoms occurring in either group. Three weeks after the last dose had been given blood was obtained and the serum examined for both H and O agglutinins. The 3-week interval was chosen because our previous studies as well as those of others had shown that a satisfactory agglutinin titer could be expected at about that period.

The examination of the sera for H and O agglutinin were conducted in the routine manner now being employed by the Pennsylvania State Health Laboratories for the H agglutinins. A standard Dreyer antigen of a Grinnell strain was employed, the tests incubated at 50° C. for 18 to 20 hours and read immediately after removal from the incubator. The highest dilution showing definite agglutination was taken as the titer. The procedure for the O agglutinin was similar except that the antigen was prepared by alcoholic extraction of a No. 305 non-motile strain. The readings were also made in the same manner.

2. Encouraged by the agglutinin response secured by subcutaneous and intracutaneous treatment with typhoid bacterin No. 97513, we proceeded with the treatment of two groups with a sensitized typhoid vaccine No. 26063, also containing 2000 million *E. typhosus* per cubic centimeter. The individuals in these groups had not previously received typhoid immunization. Bleedings were made before treatment and again 3 weeks after treatment. One group, designated as Group 1 and consisting of 19 members, received 0.5 cc., 1 cc., and 1 cc. at weekly intervals subcutaneously. Another group, designated as Group 2 and consisting of 9 members, received 0.1 cc., 0.15 cc. and 0.2 cc. at weekly intervals intracutaneously. The

bleedings obtained before and those obtained after treatment of both groups were separately pooled and tested for protective value by mouse protection tests. The protection values of the "before" and "after" sera of Group 1 and the protective value of the "before" and "after" sera of Group 2 are shown in Table 2. In the protection tests 0.1 cc. of serum was injected intraperitoneally into mice, followed in  $\frac{1}{2}$  hour by varying concentrations of typhoid bacilli. A similar test was done upon each of 5 mice and the duration of survival noted. A pooled serum of 4 patients who previously had had typhoid fever was used as a control; in addition, the same number of organisms used as a test was injected into control mice without the addition of serum. Pooled sera were used in these experiments because of the fact that an enormous number of mice would have to be used if each individual serum was to be tested.

After a rough estimate of the protective dose was obtained by the above method, additional mice were treated with serum and culture in the manner indicated in Table 3, in order to obtain a somewhat clearer end point.

TABLE 1.

Agglutinating titer of group never previously immunized against typhoid 3 weeks after receiving *subcutaneously* at weekly intervals 0.5 cc., 1 cc. and 1 cc. of typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cc.

No.	Ant.	0.	20.	40.	80.	160.	320.	640.	1280.	2560.	Av.
45	"H"	0	0	0	1	1	11	15	12	5	921
45	"O"	10	6	9	11	3	3	1	2	0	155

Agglutinating titer of group never previously immunized against typhoid 3 weeks after receiving *intracutaneously* at weekly intervals 0.1 cc., 0.15 cc. and 0.2 cc. typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cc.

No.	Ant.	0.	20.	40.	80.	160.	320.	640.	1280.	2560.	Av.
56	"H"	0	0	0	2	3	12	17	11	11	1028
56	"O"	12	12	9	9	3	6	5	0	0	123

**Results. Antibody Studies.** These are indicated in the accompanying tables. As indicated in Table 1, the H agglutinin response of individuals treated with bacterin No. 97513 was quite satisfactory in both subcutaneously and intracutaneously treated groups, with a little better response possibly in the intracutaneously treated group, since 11 of the latter sera showed a titer of 2560, as contrasted with only 5 of the subcutaneously treated group. The O agglutinin response was much lower in both groups, being possibly somewhat less in the subcutaneously treated group. This low titer for O agglutinin is in accord with the experiences of others (except Perry) after typhoid vaccination.

It was hoped that by administering one dose of vaccine (0.1 cc. intracutaneously or 1 cc. subcutaneously) to sufficient number of individuals previously vaccinated, additional evidence would be obtained to substantiate the findings of Perry as to re-vaccination. Antibody determinations were obtained only on 4 individuals in each group. These showed rather high agglutination titers (640, 640, 1280 and 1280 in intracutaneous group; 320, 640, 1280 and 1280 in subcutaneous group). This, of course, suggests a good response but is too small a group to warrant definite conclusions.



Table 2 shows the results of the protection tests on the two groups receiving sensitized vaccine No. 26063. It is to be observed that the intracutaneously treated group showed up a little better than

TABLE 2.

Results of protection tests of pooled blood taken before and after treatment with sensitized typhoid vaccine No. 26063, 2000 million *E. typhosus* per cc.

Group.	Treatment status.	Test dose.		Survival (S) or hours after test mice died.					Protection against.
		Serum, cc.	M.l.d.						
1 Subcutaneous vaccine	Before	0.1 0.1	100 1,000	16 16	16 16	16 16	24 16		None
	After	0.1 0.1 0.1	100 1,000 10,000	S 16 16	S 16 16	S 16 16	S 16 16		100 m.l.d.'s
2 Intracutaneous vaccine	Before	0.1 0.1	100 1,000	16 16	24 16	24 24	40 24	S 24	None
	After	0.1 0.1 0.1	100 1,000 10,000	S 16 16	S 24 16	S 24 16	S S 16		Between 100 and 1000 m.l.d.'s
Typhoid recovered		0.1 0.1 0.1	100 1,000 10,000	S 16 16	S 16 16	S 16 16	S 24 16		100 m.l.d.'s
5000 <i>E. typhosus</i> 50,000 <i>E. typhosus</i> 500,000 <i>E. typhosus</i> 5 million <i>E. typhosus</i>				16 16 16 16	24 16 16 16	24 24 16 16	40 24 16 16	S 24 16 16	5000 <i>E. typhosus</i> = 1 m.l.d.

History of Culture used in Mouse Protection Tests.  
*E. typhosus* Stock Culture No. 2447 (U. S. Army Panama Carrier Strain).  
 3 hours. Culture in Hygienic Laboratory Broth.  
 Culture diluted to 1000 million per cc. in 6% mucin.  
 Injection dose, 0.5 cc.

TABLE 3.—SUMMARY OF PROTECTION TESTS.

Group.	Treatment status.	Test doses.		Result.			Protection against.
		Serum, cc.	M.l.d.	Survival.	Death.	Survival, %.	
1 Subcutaneous vaccine	Before	0.1 0.1 0.1	100 500 1,000	0 0 0	10 5 10	0 0 0	None
	After	0.1 0.1 0.1 0.1	100 500 1,000 10,000	10 1 1 0	0 4 9 5	100 20 10 0	Sl. more than 100 m.l.d.'s
2 Intracutaneous vaccine	Before	0.1 0.1 0.1	100 500 1,000	2 0 0	8 5 10	20 0 0	Less than 100 m.l.d.'s
	After	0.1 0.1 0.1 0.1	100 500 1,000 10,000	10 3 4 0	0 2 6 5	100 60 40 0	More than 100 but less than 500 m.l.d.'s
Typhoid recovered		0.1 0.1 0.1 0.1	100 500 1,000 10,000	6 0 0 0	4 5 10 5	60 0 0 0	Slightly less than 100 m.l.d.'s

the subcutaneously treated group and seemed even slightly better than that of the recovered typhoid patients. When these sera were subjected to further study as indicated in Table 3, it is evident that the serum of the subcutaneously treated group had protective power against very slightly more than 100 m.l.d.'s of typhoid bacilli, whereas that of the intracutaneously treated group had protection against definitely more than 100 and slightly less than 500 m.l.d.'s. It is interesting to note that the protection in the latter group was greater than that of the convalescent typhoid sera.

*Reactions.* These as a whole were distinctly less marked in the intracutaneous group, a finding which is in accordance with our previous experience. The local reactions usually were quite mild and only in one instance was it sufficient to cause much discomfort. Except for slight nausea in one instance, mild vertigo in a second and slight general malaise in a third, no other constitutional symptoms were noted after a total of 168 doses had been given to the intracutaneous group. None of these individuals were in any way greatly incapacitated by these reactions.

The reactions, both local and general, in the subcutaneous group were much more marked. Headache, fever and malaise, lasting 48 hours, occurred in 5 instances; headache and malaise alone in 3 other instances and urticaria in 1. Most of these occurred after the second dose of 1 cc.

*Comment.* The results of these studies confirm our previous observations of the efficacy of intracutaneous typhoid vaccination, even though at present 3 doses (0.1, 0.15 and 0.2) were used in place of the original 4 doses. The agglutinin responses, both H and O, were just as good or even a trifle better after intracutaneous injection than after subcutaneous administration. The somatic or O agglutinins were also stimulated in both methods but not to as great an extent as the H type: this conforms to the experience of Dulaney and his co-workers<sup>2</sup> but is contrary to that of Perry<sup>7</sup> who found that these antibodies were stimulated to as great a degree as the H.

The results of the mouse-protection tests are quite interesting. They indicate that the protective power of the blood likewise is increased by typhoid vaccination and that here again, the intracutaneous method shows up better than the subcutaneous. It is to be admitted, since we had to use pooled sera in our experiment because of the expense entailed, that these tests can only be considered as rough guides or indicators of protective power; however, since this lack of sensitiveness applied equally to both groups, it still furnishes valuable evidence as to the efficacy of the intracutaneous method. It is interesting to note in passing that the protective power of the blood was better in both vaccinated groups than that of the blood of patients who previously had typhoid fever.

Although the number of cases was small, the fact that 8 previously vaccinated individuals showed such good antibody response after

the injection of a single dose of vaccine (0.1 cc. for intracutaneous and 1 cc. for subcutaneous group) helps to confirm similar findings by Perry and indicates that this method may be used to advantage in typhoid re-vaccination.

Finally, the marked difference in the degree of reactions in the two groups as well as the almost complete elimination of annoying constitutional symptoms in the intracutaneous group confirms the author's original observation of the advantages of the intracutaneous method of vaccination over the other routes of injection.

**Conclusions.** Further studies of intracutaneous typhoid vaccination confirmed the author's original observations as to the efficacy of this method, both from an immunologic standpoint as well as in the marked reduction of complete elimination of annoying reactions. In addition, evidence of satisfactory increase of the protective power of the blood and of stimulation of the somatic or O agglutinins was provided.

On the basis of these results, it is believed that the intracutaneous injection of 0.1 cc., 0.15 cc. and 0.2 cc. of the ordinary typhoid vaccine is the most satisfactory of any of the methods for typhoid immunization and should be more widely used. A single dose of 0.1 cc. seems adequate for immunization of previously vaccinated persons.

Finally, the author wishes to express his grateful appreciation to Dr. Wenger, Dr. Ginsburg and all the others whose help was so invaluable in the technical performance of these studies.

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## THE NATURAL HISTORY AND DIAGNOSIS OF GASTRIC ULCER.\*

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ULCER, carcinoma and chronic gastritis are the three organic diseases of the stomach that most often produce "indigestion." In

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our out-patient gastro-intestinal clinic each of these affections has accounted for approximately 4% of the cases with that syndrome; all together, for fewer than have been attributed to purely functional gastric disorders (17.5%). The truly common causes are extra-gastric, chiefly gall bladder disease, which has been responsible for 31%, and duodenal ulcer, responsible for 25%.

In spite of its comparative rarity clinically, in this country at least, gastric ulcer deserves and has received a great deal of attention because of the serious character of its complications and because of its similarity to that far more commonly recognized extra-gastric lesion, duodenal ulcer, with which it is confused and from which symptomatically it cannot be differentiated. The Quarterly Cumulative Index Medicus still groups the two diseases together, under the heading of peptic ulcer, and most authors, in their discussions of the etiology, diagnosis and treatment, do not clearly distinguish them. Although we must admit many similarities both pathologically and clinically, yet it is believed that some focusing of attention on gastric ulcer alone brings out certain important differences in the two diseases and clarifies thought about each of them.

Gastric ulcer, as a matter of fact, until comparatively recent years was not regarded as a particularly infrequent disease, and still is not so regarded in England. In Osler's System, C. F. Martin<sup>4</sup> 25 years ago stated that it was more common than duodenal ulcer in the ratio of 2 or 3 to 1. More recent roentgenologic study, however, has led us to believe the duodenal lesion to be 6 to 10 times as frequent. This change in our viewpoint is not due merely to the discovery that many of the ulcers formerly diagnosed as gastric were really duodenal, because the older statistics were based largely on objective findings at autopsy. Even modern necropsy reports support the claims of the older clinicians. Sturtevant and Shapiro,<sup>7</sup> in 1926, reviewing the records of 7700 autopsies at the Bellevue Hospital found almost 3 times as many healed and unhealed gastric as duodenal ulcers. Furthermore, Portis and Jaffe,<sup>6</sup> just a year ago, in a study of 9171 consecutive necropsies at the Cook County Hospital, found peptic ulcer in 457 cases about equally divided between the two organs. When the ulcer was an incidental finding, not related to the cause of death, they found that the gastric localization predominated; when it was acute, that it involved the stomach 4 times as often. Of the 118 essential ulcers, presumably diagnosed antemortem, the duodenum, however, was more often involved (63 to 55). Many of the acute lesions obviously heal without having produced symptoms, such as to lead to Roentgen examination, or our present roentgenologic methods fail to detect them. Furthermore, the symptoms and signs of many terminal and incidental gastric ulcers are presumably overlooked because of the predominance of other and more serious lesions. With the development of gastroscopy, however, we are beginning to appreciate the frequency

of superficial ulceration in connection with diffuse inflammatory lesions of the stomach. Thus, although duodenal ulcer is more easily and far more frequently recognized clinically, we must at the same time remember that the actual incidence of gastric ulcer is greater than our clinical data indicate, and that this is due, in part, to its occurrence in the acute form without symptoms and, in part, to its development in association with other and more serious intra-gastric and extra-gastric disease processes.

In order to get some first-hand information on the natural history and diagnosis of gastric ulcer we have reviewed the data on 111 cases observed in the medical clinic of our hospital during the last 10 years, and have included, for parts of the analysis to follow, data on 58 operatively proved cases, also from our hospital and reported in 1929 by Miller, Pendergrass and Andrews.<sup>3</sup> Thus the total series consists of 169 cases, all of which were diagnosed at operation or by the Roentgen ray. Naturally such a study does not include cases of the acute variety that give rise to no symptoms and heal spontaneously or the more chronic cases in which the presence of ulcer is masked by a more serious disease, but only such hospitalized and ambulant cases as we have been able to recognize clinically.

The sex and age incidences in the affected subjects deserve consideration because they differ from the accepted conception about them. Although the female sex has been said by some to be more commonly affected, 88% of our clinical group were in men (Tables 1 and 2). The age, furthermore, was more advanced than is generally believed, and was such as to eliminate this factor from consideration in the differentiation from gastric malignancy. At the time of examination, 67% were 40 or more years of age with the greatest incidence in the fifth decade (Table 1); this is slightly greater than for a comparable series of duodenal ulcer cases. Even if the age at the onset of the symptoms is considered this relationship still holds (Table 2). The women on the average were considerably older than the men.

TABLE 1.—AGE INCIDENCE, BY SEX, AT THE TIME OF ADMISSION TO HOSPITAL.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10-19 . . .	1	0.7	..	..	1	0.6
20-29 . . .	17	12.1	3	10.4	20	11.8
30-39 . . .	33	23.6	2	6.9	35	20.8
40-49 . . .	39	27.9	6	20.6	45	26.6
50-59 . . .	28	20.0	8	27.6	36	21.3
60-69 . . .	17	12.1	8	27.6	25	14.8
70-79 . . .	5	3.6	2	6.9	7	4.1
Total . . .	140	100.0	29	100.0	169	100.0

Recently, due largely to the influence of George Draper, we have become interested in the constitutional background of peptic ulcer, not only as an etiologic or diagnostic factor but also from the point

of view of its natural history. No one today questions that there is a physical, mental and emotional type of person who is predisposed to this disease. Draper's studies, however, were made on peptic ulcer subjects, gastric and duodenal, and probably largely duodenal, though he does not state the percentages. We suspect that if the two groups were separated not so many of the gastric ulcer patients would be found to be of the gracile, lantern-jawed, sensitive and nervously tense type, and yet such of our records as contained a statement as to body habitus indicate that 35% were of the so-called ulcer type, while only 12% were sthenic. We must admit, furthermore that many of them developed their ulcer when under great emotional strain: such strain may be effective only when the subject on some constitutional basis is predisposed. Constitutional equipment may also explain the hereditary tendency and the occurrence of ulcer in various members of a family. A family history indicative of ulcer was obtained in 14% of our patients.

TABLE 2.—AGE INCIDENCE, BY SEX, AT THE TIME OF ONSET OF SYMPTOMS.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10-19 . . .	5	3.6	1	3.3	6	3.5
20-29 . . .	29	20.7	3	10.4	32	19.0
30-39 . . .	36	25.8	3	10.4	39	23.1
40-49 . . .	29	20.7	9	31.0	38	22.5
50-59 . . .	26	18.6	8	27.6	34	20.1
60-69 . . .	12	8.5	3	10.4	15	8.9
70-79 . . .	3	2.1	2	6.9	5	2.9
Total . . .	140	100.0	29	100.0	169	100.0

Average duration of symptoms on admission = 4 years.

A further item of evidence in favor of a constitutional factor for gastric ulcer in general is its frequent association with duodenal ulcer (17% in our group). Its association with other disease processes, such as those of the cardio-vascular, renal and nervous systems, and with carcinoma elsewhere in the body at least deserves mention and probably indicates the importance etiologically of impaired general bodily vigor. Duodenal stasis was demonstrated in 4% of our series and this also may be of etiologic significance.

Of the clinical cases of advanced gastric ulcer a surprising number heal under the influence, or perhaps it is fairer to say during the course, of a simple medical regimen. That such healing occurs is shown conclusively by the large scars previously referred to as having been observed at autopsy. Of our 111 cases, 79 were given a prolonged trial on a conservative medical program with at least temporary success in 63 (80%). Satisfactory follow-up roentgenologic investigation was accomplished in but 41 of these cases but it showed a complete disappearance of the niche within 1 to 3 months in 20 (49%), in 2 of which carcinoma had originally been suspected. Eleven others showed almost a complete disappearance;

7, a satisfactory decrease in size. In some instances the defect, even though at first quite large, could not be found after 2 to 3 weeks and no subsequent interruption in the passage of peristaltic waves could be detected. Some such cases have been followed for 5 to 7 years without a recurrence of subjective or objective evidence of activity. The fact that during the past 5 years we have subjected to surgery only one-half as many patients (25%) as during the preceding 5-year period indicates our increasing personal belief that clinical cure on a conservative basis is often attainable.

In spite of such encouraging results from medical management we still feel that, because of the possibility of malignancy, every case that fails to show an actual decrease in the size of the niche by Roentgen study within 2 to 3 weeks, no matter what the other conditions may be, deserves and demands prompt surgical exploration. Although we have, of course, excluded from the group under consideration those cases that proved to be malignant, some of the included number were denied a prolonged trial of medical therapy because of that possibility. Of 19 other cases, however, that were given a reasonable trial on a conservative basis and failed to improve, 4 had organic pyloric stenosis, 4 had gastric hyperacidity (not common in gastric ulcer), 13 were excessive users of alcohol or tobacco and 2 had duodenal stasis. We are inclined to believe that all of these are unfavorable factors for the healing of gastric ulcer.

Gastric ulcer, once healed, has a tendency to recur, as does duodenal ulcer, and this took place in 38% of 47 carefully followed cases. The precipitating factors seemed to be the same as those that produced the original lesion: indiscretions in diet, alcoholic excesses, nervous or emotional strain and infection. We have noted especially their recurrence after an upper respiratory infection. As to chronic focal infection we have observed no greater incidence in ulcer patients than in those with other diseases.

Sooner or later most of the gastric ulcers that do not heal develop complications: perforation, hemorrhage, stenosis or malignant degeneration (Table 3). Also, without actual perforation, the inflammatory reaction may extend beyond the stomach and involve such structures as the pancreas or intestine, giving rise to pancreatitis, adhesions, fistulæ and even intestinal obstruction.

TABLE 3.—INCIDENCE OF COMPLICATIONS IN TOTAL GROUP OF 169 CASES.

Complication.	Per cent.
Perforation . . . . .	11
Hemorrhage . . . . .	19
Stenosis (marked and organic) . . . . .	4
Malignancy . . . . .	0.9

Perforation occurred in 19% of our previously reported 58 cases, all of which, however, were eventually surgical; whereas the incidence was only 7% in our 111 cases studied primarily on a medical

service. The incidence for the total group was 11%. Only a few occurred without preceding ulcer symptoms, but in most instances such symptoms had been present less than a year. These ulcers were almost without exception on the anterior wall of the stomach.

Gross hemorrhage at one time or another in the life history of gastric ulcer is considered to occur in about 20%. Hurst<sup>2</sup> encountered it in 18%, which closely approximates the incidence in this series (19%). Hematemesis occurred in all but one of the bleeding cases.

Stenosis, when permanent, results from fibrosis and contraction about a pyloric or antral ulcer and consequently is encountered during or after healing, often after repeated periods of activity; when transient, it is explainable on the basis of an acute inflammatory reaction or of edema, as when the blood serum protein is reduced. Severe obstruction occurred in only 4% of our series. More often it results from duodenal ulcer; though the mistake of calling these stenosing duodenal lesions gastric is very common.

Ever since the statement of McCarty's original thesis that 68% of gastric ulcers are precancerous lesions, there has been a great deal of debate as to the actual frequency of this complication. Hurst estimated it was 6%. Recently Hinton and Trubek,<sup>1</sup> reviewing 104 cases, failed to find a single one with true malignant degeneration. In our series, only 1 case developed eventually malignancy in the border of an ulcer which had been present clinically for many years. Malignant degeneration undoubtedly occurs, but we have never seen any but the one ulcer that persisted for a long time, obviously as a benign lesion, take on malignant characteristics. We have seen many ulcerative gastric lesions, especially of the pylorus, that were clinically of uncertain nature and that proved to be malignant at operation. It is difficult to prove, however, that these were not malignant from the beginning. If ulcers of the pylorus frequently become malignant, one would expect that many of the cases subjected surgically merely to a gastro-enterostomy, because of the surgeon's belief that the lesion was benign, would ultimately develop cancer of the stomach. This, we believe, has only rarely occurred.

A clear conception of the diagnostic problems of gastric ulcer requires a familiarity with its natural history. If one knows the type of individual in which, and the circumstances under which, peptic ulcer commonly develops; if he appreciates the frequency of its occurrence without clear clinical manifestations, its tendency to persist together with a capacity to heal quickly and its liability to a recurrence of activity, and if he remembers the nature of its complications he is prepared to suspect its presence when any patient presents digestive symptoms that are not readily explainable on an obvious basis. Such a suspicion of the disease is the most important factor in the diagnosis and it should, in every instance,



lead to a roentgenologic investigation. Only by such a study can the diagnosis of peptic ulcer be made or eliminated with reasonable certainty; furthermore, such an examination usually establishes definitely whether it is gastric or duodenal and the exact localization within either organ. In Table 4 it will be seen that the Roentgen diagnosis in 80 proved cases of gastric ulcer was correct in 92%.

TABLE 4.—ROENTGENOLOGIC DIAGNOSIS IN 80 PROVED CASES OF GASTRIC ULCER.

Roentgen ray diagnosis.	No.	Operative or gastroscopic findings.
Ulcer of the lesser curvature	43	36 on lesser curvature; 3 on post. wall, 4 seen by gastroscop.
Ulcer of the greater curvature	3	1 on greater curv., 1 at pylorus, 1 proved gastroscopically.
Gastric ulcer, location not stated	4	1 each on lesser curv., greater curv. and post. wall. 1 not stated.
Ulcer probably on posterior wall	4	3 on post. wall (1 proved by gastroscop.); 1 on lesser curv.
Pyloric ulcer	4	2 pyloric, 2 prepyloric.
Gastric ulcer or adhesions	5	1 hour-glass stomach, 1 lesser curv., 1 pyloric, 2 not stated.
Pyloric obstruction from ulcer	4	3 gastric ulcers with pyloric stenosis, 1 post. wall.
Marginal ulcer	2	2 lesser curvature.
Gastric ulcer or subtotal gastrectomy	2	2 lesser curvature.
Gastric ulcer or carcinoma	3	2 lesser curv., 1 large benign ulcer posterior wall.
Duodenal ulcer	1	1 lesser curvature.
Stomach negative	5	3 lesser curv. (1 perf.), 1 benign ulc. tumor, 1 seen gastroscopically.

Diagnosis correct in 92% of cases.

The history alone, when it includes epigastric discomfort in a fixed relationship to food and relief by food and especially when it covers a period of years with prolonged asymptomatic intervals, may indicate the diagnosis, but this today should never be accepted as a substitute for Roentgen identification. The physical examination, important as it is to eliminate other lesions, rarely aids greatly in the exact diagnosis of an uncomplicated case. Determination of the acidity of the gastric contents, helpful in duodenal ulcer, cannot be considered of much value in gastric ulcer. The incidence of hyperchlorhydria (Fig. 1) is only slightly higher than that frequently found in normal individuals. Achlorhydria occurred in 6% of our cases, even after histamine. Interestingly the achlorhydria cases were on the average 10 years older than the rest of our group. Most of them were at first suspected of having a malignant ulcer, but none, so far as we know, has developed convincing signs, though half of them have been carefully followed for more than a year. All responded satisfactorily to a medical regimen.

Gastroscopy deserves consideration as a diagnostic procedure. It was employed in but 12 of our cases but by means of it the diagnosis was established in 9. Certainly in those cases in which the diagnosis is suspected but the Roentgen examination is negative

or questionable, its aid should be invoked. Schindler<sup>5</sup> claims that in a series of 50 cases the diagnosis was made gastroscopically in 6 that had a negative Roentgen study.

With the natural history of gastric ulcer in mind, the diagnosis of the complications should present little difficulty. Perforation and hemorrhage are dramatic events but, in our experience, only rarely occur as the initial manifestation of ulcer. Even when perforation does so occur, the character of the attack, the physical

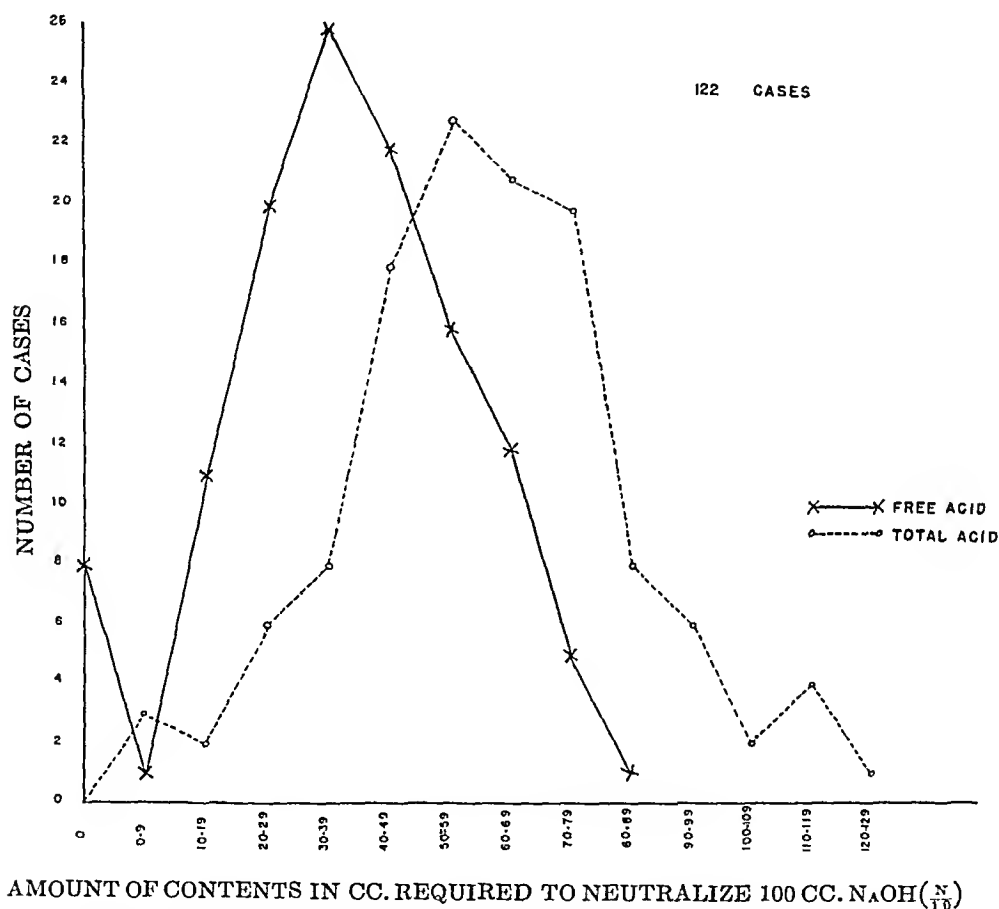


FIG. 1.—The maximal free hydrochloric acid and total acidity of the gastric contents in 122 of the cases of gastric ulcer.

signs and the demonstration, by the Roentgen ray, of air under the diaphragm is sufficient to establish the diagnosis. Since two-thirds of all massive hemorrhage from the stomach is due to peptic ulcer and most of the others to splenic anemia or cirrhosis of the liver, usually easily recognized conditions, we are rarely in doubt as to the cause of such bleeding. Stenosis, though easily recognized by gastric analysis or the Roentgen study is not always of a permanent nature and its pathology, whether acutely inflammatory,

cicatricial or purely edematous as a result of serum protein loss from the blood, deserves special diagnostic study. Malignancy, as stated before, must always be considered and can usually be diagnosed on the basis of the response to medical therapy as determined by repeated roentgenologic investigations.

**Summary.** The natural history and diagnosis of gastric ulcer have been considered in connection with an analysis of certain data from the records of 169 personally observed cases. The results suggest:

1. That gastric ulcer deserves attention apart from duodenal ulcer;
2. That it often is unrecognized clinically: sometimes because it presents no symptoms, sometimes because the symptoms are masked by those of other more serious disease processes;
3. That healing tends to occur naturally and, even in the recognized and treated cases, usually occurs on a simple medical regimen;
4. That, however, a recurrence of activity is common (38% of our carefully observed cases) and may be precipitated by such factors as gastric hyperacidity, dietary indiscretion, the excessive use of alcohol, emotional upset, or infection;
5. That the diagnosis of gastric ulcer and of its complications will be most readily made by those who have knowledge of its natural history and who subject promptly all questionable cases to roentgenologic and gastroscopic investigation.

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### EVIDENCE REGARDING THE CONTROL OF HEPATIC GLYCOGENOLYSIS.

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ARE there glycoscretory nerves distributed to the liver cells? Older investigators found that section of the splanchnic nerves prevented the "puncture diabetes" of Claude Bernard, and they drew the conclusion that these were the secretory nerves. In 1894, Cavazzani<sup>10</sup> thought he had brought proof for this view by finding less glycogen in the liver, when it was stimulated from the celiac plexus after death, than was present before the stimulation began. Wertheimer and Battez<sup>23</sup> pointed out, however, that the result

could be explained by *postmortem* glycogenolysis. Meanwhile, Kaufmann<sup>13</sup> had shown that cutting the hepatic nerves did not prevent *piqûre* from having its usual hyperglycemic effect. In 1901, Blum<sup>1</sup> reported his important observation that subcutaneous injections of adrenaline produced hyperglycemia and glycosuria. Thereupon Mayer<sup>17</sup> raised the question whether Bernard's *piqûre* might not induce glycosuria by causing a discharge of adrenaline from the adrenal medulla. After producing *piqûre* glycosuria in all 6 rabbits tested, he removed the adrenals from 25 rabbits, and found that *piqûre* did not cause glycosuria in any of them. Three years later Gautrelet and Thomas<sup>11</sup> reported that splanchnic stimulation in adrenalectomized dogs did not provoke a glycosuria. In 1912, Macleod and Pearce<sup>16</sup> confirmed these observations by showing that when in dogs the adrenal gland is removed on one side splanchnic stimulation on that side is not followed by the usual hyperglycogenolysis. They found, however, that when they excited the hepatic plexus they elicited a marked hyperglycemia, but only if the adrenal glands were intact. The opinion was ventured that "some influence exercised by the adrenal glands is evidently essential for the functional integrity of the nerves which control the process of glycogenolysis." These observations still left a function for the nerves to perform in liberating glucose from the hepatic stores.

In a study of reflex hyperglycemia Griffith<sup>12</sup> to some degree supported earlier conclusions, but he also raised puzzling questions. Stimulation of afferent nerves produced a prompt increase of blood sugar. This effect was not decreased by cutting hepatic nerves; on the average it was reduced, however, but not abolished, if the adrenals were excluded from action. And in animals with hepatic nerves severed and adrenals excluded, afferent nerve stimulation still had as great an effect as when the adrenals alone were out of function. Here is evidence that the nervous influences on the liver are effective, though of minor importance, but the problem is presented of accounting for glycogenolysis when both nervous and humoral (medullary-adrenal) agencies are inoperative.

Further testimony regarding control of liver glycogen was offered by Bulatao and Cannon<sup>5</sup> in observations on cats exhibiting "sham rage." The signs of rage in these decorticated animals, out of anesthesia, was attended by a gradually increasing hyperglycemia which might rise to 500 mg. %. If the hepatic nerves were severed, without disturbing the adrenal glands, there was still a rise in the glycemic level during the period of pseudoaffective activity. On the other hand, when the possibility of adrenal participation was excluded, the initial hyperglycemia (due to operative procedures) declined during the period.

The observations of Britton<sup>3</sup> on emotional hyperglycemia were quite in harmony with those on "sham rage." Increases of blood sugar, ranging from 30 to 90% in normal unanesthetized animals,

were noted after 2 minutes of excitement. When the liver nerves had been cut, and the adrenals left innervated, the effects of excitement were only slightly modified. Conversely, when functioning of the adrenal medulla had been excluded, emotional states, quite as intense as in normal animals, were usually accompanied, not by an increase, but by a decrease, of the blood-sugar concentration. The decrease might persist for 20 minutes or longer.

The foregoing evidence, favorable in some instances to direct nervous control of hepatic glycogenolysis and in other instances to hormonal control alone, through medulliadrenal secretion, is matched by discordant testimony of histologists. Riegele<sup>21</sup> has described a network of extremely delicate nerve filaments between the liver cells, with offshoots reaching into the cellular cytoplasm. This observation, if correct, would establish a basis for immediate nervous government of liver function. The existence of a nervous "terminal reticulum," however, has been questioned by Nonidez,<sup>20</sup> who reports that the silver method used by Riegele to stain nerve fibers may also impregnate fine connective tissue strands and thus confuse the picture. "Up to the present," Nonidez declares, "no nervous structure resembling a network has been described in the liver." This testimony would leave the management of liver functions to physical and chemical agencies operating in the blood supply.

Recent experiments, performed by Cannon and Lissák,<sup>8</sup> have brought support to the inference that glycogenolysis is not controlled by direct action of nerve impulses on liver cells. These investigators demonstrated a substance, in all respects like adrenaline in its effects, which can be extracted from the ultimate sympathetic neurones, whether these neurones, or parts of them, are isolated or are embedded in organs (*e. g.*, the heart). The significant fact appears that whereas extracts of liver blood-vessels raise blood pressure, dilate the pupil and augment cardiac contraction, extracts of liver pulp have little or no adrenaline-like action. In consideration of the difficulty of removing the pulp from the vessels without pulling away vascular twigs, the occasional slight action of the pulp is explicable without need of assuming presence of sympathetic endings on the hepatic cells. In view of the enormous numbers of these cells and the small size of the nerves which accompany the hepatic artery, it is obvious that the fibers in these nerves would have to branch to an almost incredible degree in order to reach to even a majority of the cellular units in the liver. Furthermore, there is no evidence that such branching occurs. Indeed, histologic studies, as Nonidez has remarked, provide no indication of an innervation of the hepatic cells.

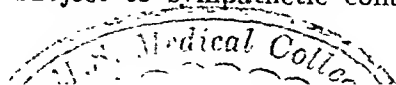
If the hepatic cells are not subject to sympathetic impulses, but are subject to secreted adrenaline, there would be explained the efficacy of *piqûre* after severance of the hepatic nerves (Kaufmann), the failure of *piqûre* to produce glycosuria in the absence of the

adrenals (Mayer), and the absence of glycosuria when the splanchnics are stimulated in adrenalectomized animals (Gautrelet and Thomas, Macleod and Pearce). There would also be explained the absence of hyperglycemia in "sham rage" (Bulatao and Cannon) and in emotional states (Britton) when the adrenal medulla is non-functional, although nerves to the liver are intact, and the marked hyperglycemia in these states when the hepatic nerves are cut and the adrenals are left innervated.

The observations of Macleod and Pearce and also of Griffith call for discussion. The former two investigators reported a notable hyperglycemia when they excited the hepatic plexus, but only when the adrenal glands were intact. It is pertinent to note that under experimental conditions there is a discharge of adrenaline from the adrenals (Cannon and Rapport<sup>9</sup>) and consequently the anesthesia and the laparotomy incidental to stimulating the nerves on the hepatic artery would have the result which Macleod and Pearce noted. If the adrenal glands were rendered inactive the same operation would be ineffective.

For an explanation of the hyperglycemia recorded by Griffith, occurring when an afferent nerve was excited even though the hepatic nerves were cut and the adrenal medulla was out of action, the experiments of Bodo and Benaglia<sup>2</sup> are significant. In 1922, Cannon and Griffith<sup>7</sup> studied the characteristics of a substance, given off from the liver when its nerves were stimulated, that was like adrenaline in causing a rise of blood pressure and an acceleration of the heart. Later (Cannon and Bacq<sup>6</sup>) such a substance was shown to be liberated into the blood stream wherever sympathetic nerves were activated and was given the name "sympathin." Under ether anesthesia its presence was difficult to demonstrate, but under chloralose it readily manifested its properties. Bodo and Benaglia, using chloralose as an anesthetic, found that sympathin produced by exciting the cardio-accelerator nerves caused hyperglycemia in animals with liver nerves and adrenals both excluded from action. And in such animals, also, they observed that emotional excitement, known to produce sympathin (Newton, Zwemer and Cannon<sup>18</sup>), induced a rise of blood sugar. Griffith employed chloralose in his experiments, and since there can be a reflex production of sympathin (Liu and Rosenblueth<sup>14</sup>), quite possibly the reflex hyperglycemia observed by him in animals with denervated liver and adrenals was due to the action of sympathin. It is noteworthy that some of the sympathin might act on coming to the liver from elsewhere, as from the heart, and some might be produced locally in the hepatic vessels and have a local effect.

In the foregoing paragraphs the main features in the evidence regarding control of hepatic glycogenolysis have been reviewed. It has been shown that the facts at hand indicate that the liver cells are not directly subject to sympathetic control, but respond to



adrenaline from the adrenal medulla, and also to circulating sympathin, by a liberation of glucose. The only anomalous feature in this situation is the existence of a highly important organ in the body, the liver, which adrenalinic readily affects, though not acting then as a sympathicomimetic agent. Pertinent to this curious anomaly is the action of ergotamine in preventing the hyperglycemia which results from cerebral lesions and from adrenaline (Nitzescu and Munteanu;<sup>19</sup> Long<sup>15</sup>). Ergotamine, as is well known, blocks the positive action of both sympathetic impulses and adrenaline in structures demonstrably innervated by sympathetic fibers.

The foregoing evidence is related to nervous management of glycogenolysis. It appears that the liver can operate satisfactorily, quite independently of that management, both to take in and give forth glucose. Soskin, Essex, Herrick and Mann<sup>22</sup> have shown, by determining simultaneously the rate of blood flow through the liver and the glucose content of the inflowing and outflowing blood, that during control periods the liver secretes glucose, but when glucose is abundantly supplied, secretion ceases and sugar is retained. And consistent with this observation, Brouha, Cannon and Dill<sup>4</sup> have recently noted that after complete removal of the sympathetic system the glycemic level is kept normal, even in vigorous exercise.

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## A SIMPLIFIED METHOD FOR CALCULATING DIABETIC DIETS.

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IN order to calculate a diabetic diet it is necessary to know the average serving in grams of the desired food, the percentage of protein, fat, and carbohydrate in each food and the customary distri-

bution of foods among the meals. This information is ordinarily readily available only to the trained dietitian.

The following plan for calculating diets is offered as a simple method which can be used with a minimum expenditure of time. Furthermore, it requires no unusual training in diet work nor further knowledge regarding foods than is possessed by most physicians. Herewith is shown the protein, fat and carbohydrate content of seven diets, increasing in each diet by 5 gm. protein, 10 gm. fat, and 25 gm. carbohydrate.\* On the following pages is shown a distribution of foods corresponding to these figures arranged in the form of diets. It will be noted that bread and butter are included in all diets. Diet No. 1 is suggested as a "starvation diet" for short-time use in order to lower the blood sugar rapidly.

TABLE 1.—SEVEN DIETARY COMBINATIONS WITH CALORIC VALUES.

	<i>Protein.</i>	<i>Fat.</i>	<i>Carb.</i>	<i>Calories.</i>
No. 1 . . . . .	50	25	25	525
No. 2 . . . . .	50	50	50	850
No. 3 . . . . .	55	60	75	1060
No. 4 . . . . .	60	70	100	1270
No. 5 . . . . .	65	80	125	1480
No. 6 . . . . .	70	90	150	1690
No. 7 . . . . .	75	100	175	1900

DIET No. 1.—(P/50, F/25, C/25—CALORIES, 525).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
½ small grapefruit . . . . .	1	..	5
or ½ medium orange . . . . .	(1)	..	(5)
or 1½ tblsp. oatmeal (cooked) . . . . .	(1)	..	(6)
1 egg plus 1 egg white . . . . .	12	6	..
2 tblsp. cream . . . . .	1	6	1
or ¼ square butter . . . . .	..	(5)	..
<i>Lunch:</i>			
1 bowl clear meat broth*			
1 egg white . . . . .	6	..	..
½ head lettuce with small amount lemon juice or vinegar . . . . .	1	..	2
4 tblsp. cottage cheese . . . . .	15	..	1
½ slice bread . . . . .	1	..	5
½ square butter . . . . .	..	5	..
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
2 oz. lean meat, fish or chicken . . . . .	12	10	..
½ slice bread . . . . .	1	..	5
	53	27	28
Coffee or tea.			
* If desired.			

\* Taken from Bull. No. 28, U. S. Dept. of Agriculture, and from "Tables of Food Values" by Alice V. Bradley.



## DIET No. 2.—(P/50, F/50, C/50—CALORIES, 850).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
$\frac{1}{2}$ cup grapefruit . . . . .	1	..	10
3 tblsp. oatmeal (cooked) . . . . .	3	..	12
1 egg . . . . .	6	6	..
1 square butter . . . . .	..	10	..
or 4 tblsp. cream . . . . .	(2)	(12)	(2)
$\frac{1}{2}$ slice bread . . . . .	1	..	5
<i>Lunch:</i>			
1 bowl clear meat broth*			
4-5 small strips bacon . . . . .	3	9	..
$\frac{1}{2}$ head lettuce . . . . .	1	..	2
2 tblsp. cottage cheese . . . . .	8	..	..
3 tblsp. 5% vegetable . . . . .	1	..	3
$\frac{1}{2}$ slice bread . . . . .	1	..	5
$\frac{1}{2}$ square butter . . . . .	..	5	
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
3 oz. lean meat, fish or chicken . . . . .	18	15	..
$\frac{1}{2}$ slice bread . . . . .	1	..	5
$\frac{1}{2}$ square butter . . . . .	..	5	..
	<hr/> 47	<hr/> 50	<hr/> 51
Coffee or tea.			
* If desired.			

## DIET No. 3.—(P/55, F/60, C/75—CALORIES, 1060).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
$\frac{1}{2}$ cup grapefruit . . . . .	1	..	10
1 medium sized orange . . . . .	..	..	(10)
3 tblsp. oatmeal (cooked) . . . . .	3	..	12
1 egg . . . . .	6	6	..
2 tblsp. cream . . . . .	1	6	..
$\frac{1}{2}$ slice bread . . . . .	1	..	7 $\frac{1}{2}$
$\frac{1}{2}$ square butter . . . . .	..	5	..
<i>Lunch:</i>			
1 egg . . . . .	6	6	..
4-5 strips bacon . . . . .	3	9	..
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
$\frac{1}{2}$ pound lean meat, fish, or chicken . . . . .	24	20	..
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
	<hr/> 55	<hr/> 62	<hr/> 78
Coffee or tea.			
* If desired.			

## DIET No. 4.—(P/60, F/70, C/100—CALORIES, 1270).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
$\frac{1}{2}$ cup grapefruit . . . . .	1	..	10
1 medium sized orange . . . . .	..	..	(10)
3 tblsp. oatmeal (cooked) . . . . .	3	..	12
1 egg . . . . .	6	6	..
4 tblsp. cream . . . . .	2	12	2
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
<i>Lunch:</i>			
1 egg and 1 egg white . . . . .	12	6	..
$\frac{1}{2}$ head lettuce . . . . .	1	..	2
2 level tsp. mayonnaise . . . . .	..	10	..
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
$\frac{1}{4}$ pound lean meat, fish or chicken . . . . .	24	20	..
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
1 medium sized orange . . . . .	1	..	10
	62	69	99

Coffee or tea.

\* If desired.

## DIET No. 5.—(P/65, F/80, C/125—CALORIES, 1480).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
$\frac{1}{2}$ cup grapefruit . . . . .	1	..	10
1 medium-sized orange . . . . .	..	..	(10)
5 tblsp. oatmeal (cooked) . . . . .	5	..	20
1 egg . . . . .	6	6	..
4 tblsp. cream . . . . .	2	12	2
1 slice bread . . . . .	2	..	15
$\frac{1}{2}$ square butter . . . . .	..	5	..
<i>Lunch:</i>			
1 egg and 1 egg white . . . . .	12	6	..
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
$\frac{1}{2}$ head lettuce . . . . .	1	..	2
2 level tsp. mayonnaise . . . . .	..	10	..
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
$\frac{1}{4}$ pound lean meat, fish or chicken . . . . .	24	20	..
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
1 medium sized orange . . . . .	..	..	10
	67	79	137

Coffee or tea.

\* If desired.

## DIET No. 6.—(P/70, F/90, C/150—CALORIES, 1690).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
½ cup grapefruit . . . . .	1	..	10
1 medium sized orange . . . . .	..	..	(10)
5 tblsp. oatmeal (cooked) . . . . .	5	..	20
2 eggs . . . . .	12	12	..
4 tblsp. cream . . . . .	2	12	2
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
<i>Lunch:</i>			
1 egg . . . . .	6	6	..
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
½ head lettuce . . . . .	1	..	2
1 level tsp. mayonnaise . . . . .	..	5	..
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
<i>Supper:</i>			
1 bowl meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
½ pound lean meat, fish, or chicken . . . . .	24	20	..
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
2 tblsp. cream . . . . .	1	6	1
1 medium sized orange . . . . .	..	..	10
	70	91	153

Coffee or tea.

\* If desired.

## DIET No. 7.—(P/75, F/100, C/175—CALORIES, 1900).

	<i>Protein.</i>	<i>Fat.</i>	<i>Carbohydrate.</i>
<i>Breakfast:</i>			
½ cup grapefruit . . . . .	1	..	10
1 medium sized orange . . . . .	..	..	(10)
5 tblsp. oatmeal (cooked) . . . . .	5	..	20
2 eggs . . . . .	12	12	..
4 tblsp. cream . . . . .	2	12	2
2 slices bread . . . . .	4	..	30
1 square butter . . . . .	..	10	..
<i>Lunch:</i>			
1 egg and 1 egg white . . . . .	12	6	
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
½ head lettuce . . . . .	1	..	2
2 level tsp. mayonnaise . . . . .	..	10	..
2 slices bread . . . . .	4	..	30
1½ squares butter . . . . .	..	15	..
<i>Supper:</i>			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6
½ pound lean meat, fish, or chicken . . . . .	24	20	..
1 medium potato . . . . .	2	..	20
2 slices bread . . . . .	4	..	30
1½ squares butter . . . . .	..	15	..
1 medium sized orange . . . . .	..	..	10
	77	100	172

Coffee or tea.

\* If desired.

In order to use the diets, find in Table 1 the diet that gives the amount of protein desired. On turning to the diet with this percentage of protein, it is evident that only bread and butter need be altered in order to arrive at the desired amount and arrangement of fat and carbohydrate. As a standard slice of bread as cut by machine contains 15 gm. of carbohydrate, and as a  $\frac{1}{2}$  inch thick slice of butter from the standard quarter-pound bar contains 10 gm. of fat, the diet given can be readily altered by the addition or subtraction of either or both of these foods.

TABLE 2.—FOOD VALUES.

	<i>Protein</i>	<i>Fat</i>	<i>Carbohydrate</i>
1 slice bread . . . . .	2	..	15
1 Uneda biscuit . . . . .	1	..	5
1 graham cracker . . . . .	1	1	8
1 medium-sized potato . . . . .	2	..	20
3 tblsp. oatmeal (cooked) . . . . .	3	..	12
1 medium-sized egg . . . . .	6	6	..
$\frac{1}{4}$ lb. lean meat, fish or chicken . . . . .	24	20	..
2 oz. cottage cheese (60 gm.) . . . . .	13	1	..
1 square butter . . . . .	..	10	..
1 tsp. mayonnaise . . . . .	..	5	..
3 strips bacon . . . . .	2	8	0
2 tblsp. 20% table cream . . . . .	1	6	1
1 glass milk ( $\frac{1}{2}$ pint) . . . . .	8	10	12
1 glass buttermilk . . . . .	8	1	12
1 tblsp. peanut butter . . . . .	5	8	3
1 tblsp. cocoa . . . . .	1	2	2
3 tblsp. 5% vegetable . . . . .	1	..	3
3 tblsp. 10% vegetable . . . . .	2	..	6

The following fresh fruits in the amounts given may be used with a food value of P/1, F/0, C/10:

$\frac{1}{2}$ cup grapefruit	1 cup strawberries
1 medium sized orange	1 slice watermelon, 6 inches by $\frac{1}{2}$ inch
1 $\frac{1}{2}$ medium sized peaches	$\frac{1}{2}$ of 4 $\frac{1}{4}$ -inch cantaloupe
1 slice pineapple, $\frac{1}{4}$ -inch thick	$\frac{1}{2}$ large apple
	$\frac{1}{2}$ banana

Water, clear broths (broths and consommé without food value, such as commercial canned broths), coffee, tea, cocoa shells, and cracked cocoa can be taken without allowance for food content.

One slice bread equals one slice from standard sliced loaf.

One square butter equals one square  $\frac{1}{2}$  inch thick from  $\frac{1}{4}$  pound bar.

Tbsp. equals one tablespoon.

Tsp. equals one teaspoon.

TABLE 3.—SUBSTITUTES.

Substitutes for 3 tablespoons cooked oatmeal:

$\frac{1}{2}$ cup corn flakes	1 cup puffed rice
$\frac{1}{2}$ cup Cream of Wheat (cooked)	1 cup puffed wheat
$\frac{1}{2}$ cup farina (cooked)	$\frac{1}{2}$ shredded wheat biscuit
2 tablespoons Grapenuts	3 tablespoons Wheatena (cooked)

Substitutes for 1 square of butter:

2 squares American pale cheese	2 $\frac{1}{2}$ squares Full Cream cheese
2 squares Cheddar cheese	2 $\frac{1}{2}$ squares Edam cheese
2 $\frac{1}{2}$ squares Roquefort cheese	2 squares Swiss cheese
2 $\frac{1}{2}$ squares Limburger cheese	3 squares Camembert cheese

Substitutes for 1 slice of bread:

1 $\frac{1}{2}$ baking powder biscuit, 2 inches in diameter	
$\frac{3}{4}$ slice Boston Brown bread, 3 by $\frac{3}{4}$ inch in diameter	
1 $\frac{1}{2}$ bran muffin, 2 inches in diameter	
1 egg muffin, 2 inches in diameter	
$\frac{1}{2}$ slice raisin bread, 4 by 4 by $\frac{3}{4}$ inch.	
1 Parkerhouse roll (large)	
$\frac{1}{2}$ slice cinnamon toast, 4 by 4 by $\frac{5}{8}$ inch	
3 pieces Melba toast, 4 by 4 by $\frac{1}{8}$ inch	
6 saltines	
3 soda crackers	
2 graham crackers	
1 cup pop corn	
2 tsp. honey	3 tsp. jam
2 tsp. maple syrup	3 tsp. marmalade
2 tsp. molasses	

TABLE 4.—VEGETABLES.

5% Vegetables.		10% Vegetables.
Artichokes	Lettuce	Beets
Asparagus	Rhubarb	Carrots
String beans	Sauerkraut	Onions
Brussels sprouts	Tomato	Green peas (canned)
Cabbage	Spinach	Pumpkin
Celery	Swiss Chard	Squash
Cucumber	Dandelion greens	Turnips
Endive	Beet greens	Mushrooms
Egg plant	Water Cress	
15% Vegetables.		20% Vegetables.
Parsnips		Potatoes
Lima beans		Shell beans
Green peas (fresh)		Boiled rice
		Boiled macaroni

In addition to the variation in the diets by the use of different meats and vegetables, further variation can be obtained by the substitution of some of the common foods listed in Table 2. Other substitutes which may be used for oatmeal, bread and butter are shown in Table 3. If a larger diet than No. 7 (P/75, F/100 C/175) is desired, bread may be added as needed. It will seldom be necessary to add protein or fat to this diet.

When these diets are used with protamine zinc insulin, a meal should be added at about 10.30 P.M., consisting of  $\frac{1}{2}$  glass milk, 3 saltines and 1 level teaspoonful of peanut butter (P/6, F/8, C/14—150 calories.)

## BOOK REVIEWS AND NOTICES

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A HANDBOOK OF ELEMENTARY PSYCHOBIOLOGY AND PSYCHIATRY. By EDWARD G. BILLINGS, B.S., M.D., M.D. Cum Laude (Ind.), Assistant Professor of Psychiatry, University of Colorado School of Medicine; Director, the Psychiatric Liaison Department of the Colorado General and Psychopathic Hospitals; etc. Pp. 271; 10 figures. New York: The Macmillan Company, 1939. Price, \$2.00.

In full accord with the teachings of Adolph Meyer, the contents are discussed under the headings of Psychobiology, Psychiatric Examination Procedures, General Psychopathology, General Principles of Psychotherapy and Selected References to Other Works Dealing with Personality Functioning and Psychiatry.

"Psychobiology is the science having to do with the study and understanding of the mentally integrated human organism." Another of the several definitions gives it as "the science and understanding of the study of both overt and implicit activity into a 'mentally integrated behavior'—normal and abnormal." Half of the volume is given to general consideration of psychopathology. Among other subjects discussed are normal and abnormal personality functioning; intellectual inadequacy reactions and constitutional psychopathic reactions; minor and major psychoses; disorientative-hallucinatory states; disorders of personality resulting from structural involvements of the brain; and psychopathologic problems of childhood. Hysterical disorders are referred to as "dissociative-dysmenseic-substitution" phenomena, and are *conversion* substitutes for repressed thoughts disturbing life experiences to which there is aversion.

While psychobiologists do not show the avidity of psychoanalysts for coining words, frequent employment of Greek derivatives, "ergasiastics" or "ergasiarty," meaning psychiatry, "holergasia," "hypothymergasia," and many more corresponding terms, may seem a bit pedantic to medical groups without psychiatric training for whom this handbook is intended. The work admirably supplements our numerous psychiatric textbooks already in use. There is an exceptionally informative index.

N. Y.

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A TEXTBOOK OF BACTERIOLOGY. The Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By HANS ZINSSER, M.D., Consulting Bacteriologist to the Peter Bent Brigham and the Children's Hospitals, Boston, and STANHOPE. BAYNE-JONES, M.D., Professor of Bacteriology and Dean, Yale University Medical School; Master of Trumbull College, Yale University, New Haven. Pp. 990; 116 illustrations. Eighth Edition, revised and reset. New York: D. Appleton-Century Company, Inc., 1939. Price, \$8.00.

THOUGH five years have elapsed since the appearance of the 7th edition, two additional copyrights in the interim show how actively this book has been sought by readers and kept up to date by the authors, in spite of the necessary increases in size and complexity. The section on pathogenic protozoa has been omitted for this edition, perhaps partly on this account, and a slight reduction in size has been obtained. The changes required by

the rapid advances in bacteriology and immunology are too numerous to mention here. They combine in maintaining this work as one of the best in its field.

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THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 23, No. 4 (Mayo Clinic Number, July, 1939). Pp. 284; 7 illustrations. Philadelphia: W. B. Saunders Company, 1939.

THIS Mayo Clinic number includes a symposium on dyspepsia, and 14 articles on miscellaneous subjects. The use of sulphanilamide, and the treatment of diabetes, syphilis, pneumonia and hypertension occupy prominent positions.

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LES INFECTIONS HUMAINES À *B. BIPOLARIS SEPTICUS* (PASTEURELLOSES). By ROBERT REGAMEY, Assistant à l'Institut d'Hygiène et de Bactériologie de l'Université de Berne et Chef du laboratoire de recherches expérimentales à l'Institut sérothérapique et vaccinal Suisse à Berne. Pp. 126; 3 illustrations. Berne: Hans Huber, 1939.

THE first part is devoted to a short description of *B. bipolaris septicus*. Part II describes experimental pasteurellosis in the rabbit, mouse and guinea pig. Part III is a critical study of pasteurellosis in humans described in the literature, and the last part is a few pages devoted to an analysis of the origin of pasteurellosis in humans. H. M.

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CLINICAL DIAGNOSIS BY LABORATORY METHODS. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, Ph.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Division on Clinical Laboratories, Mayo Clinic. Pp. 841; 368 illustrations (29 in colors). Ninth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1939. Price, \$6.00.

THIS excellent manual, of which a new edition has appeared every 3 or 4 years, continues to offer a wealth of well-considered, accurate information for workers in the clinical laboratory.

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JOHN HOWARD (1726-1790). HOSPITAL AND PRISON REFORMER: A BIBLIOGRAPHY. By LEONA BAUMGARTNER, M.D., Ph.D., with Introduction by ARNOLD M. MUIRHEAD, M.A. (OXON.). Pp. 79; 9 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.00.

THE philanthropist John Howard should be revered for his years of struggle for the improvement of public health as well as for prison reform. Modestly calling himself a plodder who collected material for men of genius to use, he spent his last 17 years searching through England, Wales and all the countries of Europe for data on the appalling conditions of prisons and hospitals, until his death of "camp fever" in Russia in 1790 while inspecting military hospitals. The present bibliography of 204 items, reprinted from the *Bulletin of Medical History*, is a scholarly production enlivened by frequent notes and a listing of the present location of known copies of his writings, and especially by the appreciative biographic introduction by A. M. Muirhead. E. K.

SYMPOSIUM ON THE SYNAPSE. By HERBERT S. GASSER, JOSEPH ERLANGER, DETLEV W. BRONK, RAFAEL LORENTE DE NÓ, ALEXANDER FORBES. (Reprinted from *Journal of Neurophysiology*, 2, 361-472, 1939). Pp. 113; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, Bound, \$2.00; Paper cover, \$1.50.

THOSE interested in neurophysiology are deeply indebted for the publication of this series of brilliant discussions of a subject of controversy so protracted and so important. The leaders in the field are here, each at his best or near it, and each writing in a manner so characteristic as to render the work as fascinating to the biographer as to the experimenter. Only one serious stricture can be laid upon it, or rather upon those responsible for the symposium—that it is not sufficiently inclusive. In a controversy we like to see both sides equally represented. Of the 5 authors, 3 argue for an electrical mechanism, 1 for a chemical, and 1 for a dualistic hypothesis. Could we have had under the same cover a discussion by Dr. Cannon or Dr. Rosenblueth, for instance, the book would have been more fairly representative of current opinion. Yet we have a feast as it is and of the best. No less churlish reviewer would grumble for more.

We cannot close without a word of gratitude for the most appropriate dedication to Sir Charles Sherrington. G. McC.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine; and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Associate in Dermatology, University of Kansas, School of Medicine. Tenth edition, revised, enlarged and reset. Pp. 1549; 1452 illustrations and 21 color plates. St. Louis: The C. V. Mosby Company, 1939. Price, \$15.00.

"Diseases of the Skin" by R. L. Sutton, Sr., has been a standard dermatologic text for about 20 years. This edition not only preserves the outstanding features of previous issues, but the father-son combination has added new ones that may establish it as the American encyclopedia of dermatologic information.

This edition not only retains the pictorial excellence for which its predecessors are known, but amplifies it by 340 new illustrations and 10 color plates. A change in type has made it possible to include 100% more text and 7000 additional references without a material increase in bulk.

Certain textual changes are noteworthy. The material has been classified on an etiologic basis and an attempt has been made to correlate cutaneous disorders with general medicine. This has called for increased space devoted to fundamental physiologic and biologic phenomena. These discussions, aided by contributions of experts in the field, are generally adequate. For ready review of certain dermatoses there are, conveniently placed, detailed lists and tables. The thoroughness of the bibliography can be judged by the section on venereal lymphogranuloma.

The authors have added valuable personal opinion and experiences to the documented statements from the literature. For example, their treatment of *acne vulgaris*, which cuts the average number of visits in half, demands immediate attention.

While the Reviewer has found little to complain of in this textbook, he would like to know why, if "pruritus" is as bad a diagnosis as "eczema," the authors still devote so extended and conventional a discussion to that "dermatological scrap-heap," eczema. A proper appreciation of the merits of the book can, of course, be obtained only by an examination of the book.

H. B.



THE HARVEY LECTURES, SERIES XXXIV. Delivered under the Auspices of The Harvey Society of New York, 1938-1939, under the Patronage of the New York Academy of Medicine by DRs. G. F. MARRIAN, A. A. WEICH, E. F. DuBOIS, E. J. COHN, E. A. PARK, K. LINDERSTRØM-LANG, C. H. DANFORTH, A. SZENT-GYÖRGYI. Pp. 279; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, \$4.00.

THIS latest volume of this famous series contains 8 lectures on such varied subjects as the steroid hormones, serum albumin, heat loss, proteins as chemical and biologic material, the pathology of rickets, tissue and cell enzymes, genic and hormonal factors in biologic processes, and biologic oxidations and vitamins. These latest words by leaders in their fields are indeed useful half-way stations between original reports and textbooks.

E. K.

GROSS ANATOMY. A Brief Systematic Presentation of the Macroscopic Structure of the Human Body. By A. BRAZIER HOWELL, Associate Professor of Anatomy, Johns Hopkins University School of Medicine. Pp. 403; 56 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, \$6.00.

THE author well states the dilemma of present-day teaching of anatomy in his introductory chapter: the time allotted for anatomy in the medical curriculum has been sharply decreased; the scope of the science has been broadened. The problem is to present enough of this increased fabric of anatomy in the decreased time so that the medical student may continue an orderly progress. This work is apparently intended as a substitute for the longer texts in gross anatomy. How complete this substitution is meant to be is not entirely obvious from the introduction; however, with but 56 illustrations the student would need to have other works constantly available. It seems questionable whether the problem of condensation is helped by devoting 111 pages to the muscular system and 266 pages to the rest of the body. As would be expected from the author's background, the section on muscles is the best feature of the book. The correlation with comparative anatomy is interesting and is attractively written. However, this division would seem to be of more value as collateral reading for the medical student than as text material. The correlations are toward the comparative rather than the medical side. Many of the references to comparative anatomy cannot be justified on grounds other than that of general academic interests. Some of them are definitely useful in simplifying the understanding of the human relationships. Should a short book endeavoring to cover the complete course in gross anatomy spend space to figure the forearm muscles of the iguana? These sidelights on human anatomy disappear in a large part in the presentation of the other systems in the body, where the style becomes almost breathless. There could be raised many minor objections to the presentation of anatomic facts, these sometimes representing a legitimate difference of opinion among anatomists. In view of the large amount of space devoted to the morphology of muscles, it is surprising that the function of the larynx in movements of the upper extremities is omitted.

O. B.

RECENT ADVANCES IN HEMATOLOGY. By A. PINEY, M.D., CH.B. (BIRM.), M.R.C.P. (LOND.), Assistant Physician, St. Mary's Hospital for Women and Children, London. Pp. 312; 34 illustrations and 8 colored plates. Fourth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, \$5.00.

THOUGH this edition has been so completely revised that it is practically a new book, it is by no means confined to "recent advances," as many

of the references will bear witness. It is rather, as stated in the first edition, an attempt to indicate "the present position of a number of hematological subjects." It doubtless will be of use to those who do not have access to recent larger and more complete works on the subject.

E. K.

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**DISEASES OF THE NOSE AND THROAT.** By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc., and HERMAN J. BURMAN, M.D., F.A.C.S., Adjunct Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc. Pp. 726; 480 illustrations. Second edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, \$7.00.

In this volume the authors present in concise form the generally accepted opinions in the field of rhinology and laryngology. The plan and form of the book follow that of the first edition published three years ago. While the text is terse and at times dogmatic, it is also explicit and thorough. The brief but adequate discussions of the embryology, anatomy and physiology of the various structures in the upper respiratory tract will appeal alike to the student, general practitioner and specialist. Considerable stress is laid upon therapeutic measures and minor technical procedures, but with the elimination of controversial matter. The illustrations are numerous, appropriate and instructive. Conscientiously assuming responsibility for systematic instruction, the authors have wisely introduced illustrations of the instruments comprising the armamentarium for various surgical procedures. Roentgen examination of the nasal accessory sinuses is treated at considerable length. The thorough and detailed treatment of such subjects as physical therapy in the nose and throat, rhinologic manifestations of general systemic diseases and laboratory aids deserves commendation. This is a well-arranged, authoritative and informative textbook.

H. S.

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**ELEMENTARY ANATOMY AND PHYSIOLOGY.** By JAMES WHILLIS, M.D., M.S., F.R.C.S., University Reader in Anatomy, Guy's Hospital Medical School; late Lecturer in Anatomy in the University of Durham. Foreword by T. B. JOHNSTON, M.D., CH.B., Professor of Anatomy, University of London. Pp. 342; 87 illustrations prepared from original drawings by PAULINE LARIVIÈRE. Philadelphia: Lea & Febiger, 1939. Price, \$3.50.

FROM the foreword by Professor Johnston and the announcement of the publisher it appears that this little book is intended for medical students as well as others beginning the study of human anatomy. The American medical student begins his study of human anatomy with a background of general biology and frequently with training in comparative anatomy. This should make superfluous the diagrammatic summary of histology. The book might be quite "effective with students in physical education and in nursing." Any short anatomy, even without physiology, must be either a dictionary-like condensation of terms or it must represent a careful selection of material. The author, obviously an experienced anatomist, has made a good selection. The presentation is handled in a conservative way, which may be the safest plan in a short anatomy. Many more pretentious works still continue to give Helmholtzian notions of ear mechanics and descriptions of the viscera based on the postmortem rather than on the living state. It is a time-honored custom to repeat illustrations, giving a different figure number. Illustration number 38 appears again as numbers 46, 55 and 60, while number 28 reappears as 53, 69 and 85. These with other repetitions reduce the total number of original figures from 87 to 69. This proportion of repetitions seems a little high. The subject matter is well organized, the definitions are clear, and the typography is such that the eye readily follows the text.

O. B.

**PERIPHERAL VASCULAR DISEASES.** Diagnosis and Treatment. By WILLIAM S. COLLENS, B.S., M.D., Metabolist, Chief of the Clinic for Peripheral Vascular Disease; Chief of the Diabetic Clinic, Israel Zion Hospital, Brooklyn, etc., and NATHAN D. WILENSKY, M.D., Assistant in Clinic for Peripheral Vascular Disease; Assistant in Diabetic Clinic, Israel Zion Hospital, etc. Pp. 243; 77 illustrations, 3 color plates. Springfield, Ill.: Charles C Thomas, 1939. Price, \$4.50.

THE publisher properly states that "this ready reference to the facts on peripheral circulation comprehensively surveys the extensive experimental and clinical literature and supplies practical information on the diagnosis and treatment of vascular disorders in a form readily available for quick reference in private practice." Its title follows common usage of the term "peripheral vascular disease" to mean "peripheral arterial disease." Nearly one-half of the book is devoted to descriptions of diseases, the rest to treatment. The former, in this Reviewer's opinion, is more successful than the latter. The authors understandably devote considerable space to intermittent venous occlusion, their new and interesting method of treatment. However, one may be skeptical about their chief theoretical basis for its use, namely, an implication that it increases average blood flow during treatment: their measurements fail to prove the point. For the most part therapeutic management of patients is capably discussed, and suitable therapy for the individual patient properly emphasized.

H. M.

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**THE RECTUM AND COLON.** By E. PARKER HAYDEN, A.B., M.D., F.A.C.S. Assistant in Surgery in the Harvard Medical School, Boston; Assistant Surgeon and Chief of Rectal Clinic, Massachusetts General Hospital, Boston. Pp. 434; 169 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$5.50.

ANOTHER book on the rectum and colon might seem to be superfluous at the moment; nevertheless, this work by Hayden is a very practical and extremely useful one. Written almost entirely in the first person, it gives the personal experience of the author rather than an encyclopedic review of the literature. The subject is approached in the conventional manner, first a chapter on anatomy, followed by chapters on methods of examination and on the significance of the usual symptoms. In the chapter on pruritus ani the author, after mentioning the necessity for the treatment of local anal lesions, recommends various antipruritic ointments. In his clinic, reliance is placed on the injection of oil-soluble anesthetics or of alcohol in small doses in scattered areas. For anal fissure a conservative operation is outlined in which the fissure is excised and the pecten band below it incised. Dilatation of the sphincter muscle is thought to be not only unnecessary but really harmful. On prolapse of the rectum, the author cites his experience and recommends the Moschowitz procedure.

For strictures of the rectum complicating lymphogranuloma, conservative therapy is advised until, or unless, more radical procedures are necessary. If colostomy alone does not effect a definite improvement, resection of the rectum is recommended.

In the treatment of rectal polyps, the author does not hesitate to make an incision into the colon to resect these potentially dangerous lesions. He does not mention the removal of polyps by the use of an electric snare, although the Reviewer believes this is the easiest and safest treatment of polyps which can be reached through the proctoscope. For carcinoma of the rectum, the author describes a standard abdominal perineal operation.

In reading this book, one is impressed by the fact that it is based on a personal experience. Statistics are given from the clinic at the Massachusetts General Hospital in discussing practically every one of the lesions.

One has the impression that he is visiting the clinic of the author and in this way is gaining a personal knowledge of his methods of diagnosis and treatment. The book is well printed and fairly well illustrated, mostly with line drawings and with photographs of lesions. The Reviewer can recommend this compact volume to those who are interested in the diagnosis and treatment of the disease of the anus, colon and rectum. L. F.

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THE NEW INTERNATIONAL CLINICS. VOL. 3 (N.S. 2), SEPTEMBER, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 332; many illustrations, 1 colored plate, Philadelphia: J. B. Lippincott Company, 1939.

THE 16 original articles and 6 "clinics" in this number are widely diversified; the Review is on obstetric hemorrhage. The volume index gives a good survey of the material covered by this excellent quarterly.

E. K.

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MATERNAL CARE AND SOME COMPLICATIONS. The Principles of Antepartum, Intrapartum, and Postpartum Care and of the Management of Some Serious Complications. Approved by The American Committee on Maternal Welfare, Inc. Edited by F. L. ADAIR, M.D. Prepared by W. C. DANFORTH, M.D., G. W. KOSMAK, M.D., R. D. MUSSEY, M.D., R. L. DE NORMANDIE, M.D., F. L. ADAIR, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 194. Chicago: The University of Chicago Press, 1939. Price, \$1.50.

THIS small volume brings together under one cover the contents of two previous volumes, one on maternal care and the other on maternal care complications, both previously reviewed in the Journal (194, 720, 1937; 197, 113, 1939). Its chief aim is to help reduce maternal mortality. It aims to summarize our current knowledge regarding the best technique for prenatal care and discusses the more common complications of pregnancy and labor, outlining the accepted methods for their treatment and prevention. It seems to be a good handbook for public health nurses, and for physicians who wish to keep abreast of current knowledge in this field.

D. M.

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THE STORY OF SURGERY. By HARVEY GRAHAM. With a Foreword by OLIVER ST. JOHN GOGARTY. Pp. 425; 24 plates and frontispiece. New York: Doubleday, Doran & Co., Inc., 1930. Price, \$3.75.

FULL advantage is taken by the pseudonymous author of this attractive book of the greater freedom permitted to a "story" than to a "history." Documentation with dates, references, and footnotes can be ignored; unsettled matters need not have both sides represented or evaluated or can readily be ignored, free rein can be given to anecdotes; completeness is not demanded and even accuracy is not as indispensable, where the chief aim is to entertain, as in a work of reference or instruction where reliability must be of prime importance. Not that the criticism of inaccuracy should be made against the author, who obviously has wide and accurate knowledge of his subject. In fact, no small part of the charm lies in the emphasis on the subjects in which the author appears to be personally interested. For this reason, perhaps, we should not object to the otherwise disproportionate space given to British contributions—both meritorious and otherwise. However, while it is good for Americans to know how much British surgery has accomplished, it is not so good for Britishers to be given such a lop-sided picture. In the four-page bibliography there is—perhaps intentionally—not one reference in a foreign language. The first 100 pages

takes us to the 13th, "greatest of centuries," whereas more than 100 are required for the 19th alone. The pictures of Paré, the Hunters, Astley Cooper, the Bells, J. Y. Simpson, and Lister are distinctly more satisfying than anything to be found in general histories. In general, we are sure that many readers will agree with Gogarty, who wrote the Foreword, "This is the best book on surgery I have ever read." E. K.

### NEW BOOKS.

*The Care of a Small Rat Colony.* By ROLLAND J. MAIN, PH.D., Department of Physiology and Pharmacology, Medical College of Virginia, Richmond; Vitamin Assay Laboratory, Department of Agriculture and Immigration, Commonwealth of Virginia. Pp. 101; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, \$2.00.

This is a reasonably complete discussion of the details of management of a rat colony giving description of rooms, cages and other equipment, feeding, breeding, and hygienic measures. The book would have been improved by more direct descriptions and some rewriting, but may be used with profit by anyone having to do with colonies of rats, or planning to start a colony. H.R.

*Sketches in Psychosomatic Medicine* (Nervous and Mental Disease Monographs No. 65). By SMITH ELY JELLIFFE, M.D., Consulting Neurologist to Manhattan State and Kings Park Hospitals, New York. Pp. 155; illustrated. New York: Nervous and Mental Disease Monographs, 1939. Price, \$3.00.

*Electrocardiographic Patterns.* Their Diagnostic and Clinical Significance. By ARLIE R. BARNES, M.D., Mayo Clinic, Rochester, Minnesota. Pp. 197; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

*Outline of Physiology.* By WILLIAM R. AMBERSON, PH.D., Professor of Physiology, University of Maryland, and DIETRICH C. SMITH, PH.D., Associate Professor of Physiology, University of Maryland. Pp. 412 (double column); 177 illustrations (15 in color) by NORRIS JONES, Instructor in Scientific Illustrating, Swarthmore College. Baltimore: The William & Wilkins Company, 1939. Price, \$4.00.

*The Electrocardiogram and X-ray Configuration of the Heart.* By ARTHUR M. MASTER, B.S., M.D., F.A.C.P., Associate in Medicine and Chief, Cardiographic Laboratory, The Mt. Sinai Hospital, New York; Associate in Medicine, The College of Physicians and Surgeons, Columbia University, New York. Pp. 222; 71 cases with 204 engravings. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

*Proctoscopic Examination and Diagnosis and Treatment of Diarrheas.* By M. H. STREICHER, M.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medical Research and Educational Hospital, and Department of Surgery, Grant Hospital of Chicago. Pp. 149; 39 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$3.00.

*The Hospital Care of Neurosurgical Patients.* By WALLACE B. HAMBY, M.D., F.A.C.S., Associate Professor of Neurology and Instructor in Surgery (Neurological Surgery), University of Buffalo School of Medicine, Buffalo. Pp. 118; 24 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$2.00.

*Manual for Diabetic Patients.* By W. D. SANSUM, M.D., Chief of the Staff of The Sansum Clinic and Director of Metabolic Research of the Santa Barbara Cottage Hospital, ALFRED E. KOEHLER, PH.D., M.D., Member of the Staff of The Sansum Clinic and Member of the Metabolic Research Staff of the Santa Barbara Cottage Hospital, and RUTH BOWDEN, B.S., Dietitian of The Sansum Clinic, Santa Barbara, Calif. Pp. 227; illustrated. New York: The Macmillan Company, 1939. Price, \$3.25.

*Endocrine Gynecology.* By E. C. HAMBLEN, B.S., M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Gynecologist in Charge of the Endocrine Division and Sex-Endocrine Clinic, Duke University Hospital, Durham, N. C. Foreword by J. B. COLLIP, M.D., Gilman Cheney Professor of Biochemistry and Pathological Chemistry, McGill University, Montreal. Pp. 453; 169 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, \$5.50.

"The laboratory investigations of the chemistry and physiology of various glandular extracts, varying as they do from the study of very simple and essentially crude extracts to those of a high degree of purity, must of necessity—in part at least—be more or less impractical. It is quite impossible to transfer at once the results of physiological studies on various animals to man even though these results may be very clear cut and readily duplicable. Everyone who has had experience in the pure physiological field is only too well aware of the tremendous differences that exist in the responsiveness of individuals of different species to the same basic hormone treatment. Probably in no branch of endocrinology is this 'species difference' more outstanding than in the field of sex physiology. Quite irrespective then of the degree of clarity that has been attained in elucidation of the physiological or pharmacologic properties of chemically pure hormones or extracts of hormones, the clinical value—if any—of such work must be determined by clinical experiment by clinicians working alone or in collaboration with their colleagues of the laboratory. It is for this reason that this volume on endocrine gynecology by Dr. Hamblen is in my opinion very timely. . . ." (From Dr. Collip's Foreword.)

*The Essentials of Medical Treatment.* By DAVID MURRAY LYON, M.D., D.Sc., F.R.C.P. Ed., Professor of Clinical Medicine, The University, Edinburgh. Pp. 448; 19 illustrations. Edinburgh: Oliver & Boyd, 1939. Price, 15/-.

#### NEW EDITIONS.

*Fractures.* By PAUL B. MAGNUSON, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School; Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Pp. 511; 319 illustrations. Third Edition, revised and enlarged. Philadelphia: J. B. Lippincott Company, 1939. Price, \$5.00.

Magnuson's new third edition of "Fractures" is thoroughly modern. It is well illustrated. The bibliography is extensive and contains important recent references. The text emphasizes the fundamental processes upon which the successful treatment of fractures must be based. This work is probably the best treatise in English dealing with fractures. G. W.

*The Merck Index.* An Encyclopedia for the Chemist, Pharmacist, Physician, Dentist and Veterinarian, Containing useful scientific data and other information on the physical, chemical and medicinal properties, as well as the various uses, of chemicals and drugs; also more than 4500 chemical clinico-chemical reactions, tests and reagents; formulas for preparation of culture media, fixatives and staining solutions; useful tables; antidotes for poisons; literature references. Pp. 1060. Fifth Edition. Rahway, N. J.: Merck & Co., Inc., 1940. Price, \$3.00.

This valuable publication, inexpensive because it is published on a non-profit basis, contains a mass of highly useful and accurate information of the kind indicated in the subtitle. The present edition represents the biggest revision that has been undertaken since the first edition appeared in 1889, almost doubling the size of the fourth edition (1930). It will be of use to physician, dentist, veterinarian, and to the laboratory worker as well as the clinician. E. K.

*Human Helminthology.* A Manual for Physicians, Sanitarians and Medical Zoölogists. By ERNEST CARROLL FAUST, A.B., M.A., Ph.D., Professor of Parasitology and Director of Laboratories, Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 780; 302 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$8.50.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE.

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UNDER THE CHARGE OF  
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### A CLASSIFICATION OF HEMORRHAGIC DISEASES DUE TO DEFECTS IN THE COAGULATION MECHANISM OF THE BLOOD.

#### BASED ON RECENTLY PUBLISHED STUDIES.

GREAT strides have been made during the past few years in the study of the coagulation of blood. Much knowledge has rapidly accumulated, and has found immediate clinical application. No comprehensive attempt, however, has been made to organize this new information or to utilize it for outlining a classification of hemorrhagic diseases which the clinician can use as a guide both in diagnosis and in treatment. The object of this review is to develop such a classification.

It is fairly well recognized as Kugelmass<sup>31</sup> pointed out, and as Madison and Squier<sup>33</sup> have recently reemphasized that the body has a dual defense against hemorrhage: the first being the coagulability of the blood, and the second, the vascular response to trauma and injury. Surprisingly, the latter factor is in all probability involved in many more bleeding conditions than is the defective coagulation of blood. The importance of the vascular defense is strikingly illustrated by a case recently described by Macfarlane.<sup>32</sup> The blood of his patient was completely lacking in fibrinogen, presumably from birth, and therefore could not clot. Nevertheless this patient had reached the age of 8 years without encountering any hemorrhage that could not be controlled.

So little is known about the fundamental factors of the vascular response that one can only recognize the existence of a group of hemorrhagic diseases, notably the purpuras, in which it is fairly certain that the basic defect is vascular. Madison and Squier hold that a group of hemorrhagic diseases are of a mixed type, *i. e.*, partly vascular and partly involving dysfunction of coagulation. Until further trenchant knowledge on this subject has accumulated, it seems futile to attempt any extensive discussion or to offer any elaborate classification of these diseases.

In regard to the first defense mechanism against hemorrhage, namely, the coagulation of the blood, sufficient data are now available to allow the formulation of a satisfactory theory to explain the coagulation mech-

anism and to use this as the basis for a classification of hemorrhagic diseases.

As the culmination of the researches begun by Alexander Schmidt and extended by the work of Hammarsten, Arthus and Pages, Pekelharing, Fuld and Spiro, Bordet, Howell, Morawitz and others,<sup>27b</sup> there has evolved a simple theory for the explanation of the coagulation mechanism, which Wöhrlisch<sup>71b</sup> has appropriately named the classical theory of coagulation. It is concisely expressed in the form of two equations:

Prothrombin + thromboplastin + calcium = thrombin

Fibrinogen + thrombin = fibrin

It can be seen that the clotting process consists of two distinct steps: first, the formation of thrombin; and secondly, the conversion of fibrinogen by thrombin to fibrin. It is important to note that only four primary factors are required for the clotting of blood, namely, prothrombin, thromboplastin, calcium, and fibrinogen; and obviously a deficiency of any one of these will wholly inhibit or markedly delay the coagulation of blood. It is therefore desirable to summarize briefly the most important facts known about these four agents in order that their significance in the various hemorrhagic diseases can be fully understood.

**Prothrombin.** This agent is the precursor or mother substance of thrombin, the active coagulating enzyme. It is believed to have the nature of a proenzyme, is closely associated with the serum protein, globulin, is inactivated at 60° C., and is removed from plasma by alumina cream, magnesium hydroxide, and other similar adsorbing agents. It is apparently found exclusively in the plasma and is not derived from the platelets as was formerly assumed.<sup>11a</sup> The view that prothrombin is combined with an antiprothrombin similar to or identical with heparin has been largely abandoned, especially since no evidence can be found that normal blood contains any anticoagulant such as heparin.<sup>47b</sup> Several methods for the determination of prothrombin have been developed. Quick's<sup>47a,49</sup> method is based on the clotting time of oxalated plasma after adding an excess of thromboplastin and a fixed amount of calcium. From the clotting time, the prothrombin can be determined by means of a chart prepared by the author. In a second method (Warner, Brinkhous and Smith<sup>67</sup>) the plasma is diluted, after which the prothrombin is converted to thrombin. From the dilution required to obtain a thrombin solution which will clot a preparation of fibrinogen in 15 seconds, the concentration of prothrombin is empirically calculated. An indirect method for determining prothrombin is employed by Dam and Glavind.<sup>11a</sup> It consists in finding the minimum amount of thromboplastin required to clot, in 3 minutes, blood to which a fixed quantity of heparin has been added.

Studies made on the prothrombin content of normal blood disclose two interesting findings: first, the constancy of the prothrombin level, and second, the large excess which is many times more than the physiologic requirements. It has been shown by Quick, Stanley-Brown, and Baneroff<sup>50</sup> that 80% of the prothrombin can be lost before the coagulation time is appreciably prolonged; and clinically it has been found that serious hemorrhage does not occur until the prothrombin sinks below 20%.<sup>6b,47f,60</sup>



**Thromboplastin.** This substance has the function of converting prothrombin into active thrombin. In this reaction ionized calcium is essential. Whether thromboplastin merely activates prothrombin, or whether it actually unites chemically is not known. Recently Eagle and Harris<sup>15</sup> have demonstrated that trypsin can change prothrombin to thrombin. This finding suggests the possibility that the action of thromboplastin may likewise be that of an activating enzyme. If this can be proved, the term thrombokinase should replace thromboplastin. In the past many other names have been applied to this agent, such as tissue extract, tissue fibrinogen, cytocyeme, thrombocyeme, cephalin, and platelet factor.

Thromboplastin is widely distributed in the body as an intracellular substance. In the blood, it occurs locked up in the platelets and perhaps is present also in the leukocytes. Certain tissues, notably the brain, lungs, and thymus, are particularly rich in thromboplastin. It apparently never occurs free, but is liberated whenever tissue cells are injured or ruptured. In blood uncontaminated by tissue juices, the thromboplastin is derived solely from the platelets. The liberation of thromboplastin from platelets, therefore, appears to be the prime factor in determining the clotting time of blood obtained by venipuncture. The slowness with which thromboplastin is liberated is illustrated by this simple experiment: On placing 1 cc. of blood obtained by venipuncture in a small test tube, it will remain liquid for 4 to 8 minutes, whereas if the same quantity of blood is mixed with a drop of an active thromboplastin solution, coagulation occurs in less than 20 seconds. Thromboplastin is fairly resistant to heat. Even on boiling for several minutes, not all of its activity is lost. Oxidation, however, destroys its potency, perhaps because of the presence of unsaturated lipoids in its molecule. It is widely accepted that cephalin is a constituent of the thromboplastin complex.

**Calcium.** For the conversion of prothrombin to thrombin, ionized calcium is essential. Whether this element is present in the thrombin molecule has not been decisively answered, but it appears certain that the presence of calcium is not needed for the action of thrombin on fibrinogen. This is the original view of Hammarsten which recently has received strong support from the careful research of Weitnauer and Wöhlisch.<sup>70</sup>

Calcium appears to play an important part in the lysis of platelets. Early workers observed the preservation of platelets in decalcified blood, and Ferguson<sup>18</sup> has convincingly demonstrated that calcium alters the platelet in such a manner that the osmotic pressure within the cell is increased thus causing it to take up water to the point of disruption. The writer recently has observed that goose blood, which will remain liquid for days, can be made to clot in a few minutes by adding a small amount of calcium chloride.

**Fibrinogen.** This exceedingly labile plasma protein has the property of being converted from a colloidal solution or sol to an insoluble gel by the action of thrombin. In this process, the fibrin forms fine needles or threads which enmesh the cellular constituents of the blood. Toeantins<sup>64</sup> has shown that platelets will attach themselves to the shaft of these fibrin threads, and in some inexplicable way cause these fibrin

strands to bend and twist thereby effecting a compression of the fibrin mass which is grossly recognized as clot retraction.

Not only do the platelets bring about the contraction of the clot, but also in some obscure manner they increase the adhesiveness of the fibrin to surfaces with which it comes in contact. The importance of this in hemostasis is obvious. The clot within the lumen of a severed blood-vessel by adhering tightly to the wall will bring about by its contraction a mechanical constriction of the blood-vessel.

Fibrinogen occurs not only in the plasma, but also in lymph, chyle, exudates and transudates. Undoubtedly this protein plays as important a part in tissue repair work as it does in coagulation.

**Thrombin.** This substance is not a primary factor, but a resultant from the interreaction of prothrombin, calcium and thromboplastin. Most investigators are accepting the view that thrombin is an enzyme which acts specifically on fibrinogen. An excellent summary of the evidence for the hypothesis has been presented by Eagle.<sup>14c</sup> Certain snake venoms such as that of the tiger snake contain a substance similar or identical to thrombin, which is responsible for their powerful coagulant action. Recently Quick<sup>47a</sup> has shown that thrombin is inactivated by serum albumin, and he has concluded that this serum protein is the normal antithrombin of the blood which is responsible for the rapid disappearance of thrombin activity in fresh serum. It should be noted that serum albumin does not inhibit the coagulation of fibrinogen, but acts only after the conversion to fibrin has been complete.

For a comprehensive understanding of the coagulation problem, it is essential to know that the clotting time is proportional to the concentration of thrombin. Fuld<sup>20</sup> expressed the relationship between the clotting time and the concentration of thrombin as follows:  $\log \frac{t_1}{t_2} = .0585 \log \frac{y_2}{y_1}$  ( $t$  = clotting time;  $y$  = concentration of thrombin).

Martin<sup>34</sup> stated it more simply:  $ty = \text{a constant}$ . Barrett<sup>4</sup> more recently has elaborated on Martin's equation. These equations unfortunately are not suitable for practical application. Recently the author found that it was possible to prepare a thrombin solution having a high and constant activity.<sup>47b</sup> When one part of this solution is mixed with two parts of oxalated plasma, a clot is formed in exactly 3 seconds. By progressively diluting the thrombin solution, the clotting time is increasingly retarded, and if the clotting times are plotted against the concentrations of thrombin, a curve is obtained, which over a wide range including the crucial portion of the curve corresponds to the equation:

$$\text{c.t.} = a + \frac{k}{c} \quad (\text{c.t.} = \text{clotting time; } c = \text{concentration of thrombin;}$$

$a$  and  $k$  constants having the value 2.38 and 88, respectively, provided the thrombin solution which causes clotting in 3 seconds is taken as 100 %.) By means of such a standard thrombin solution, any blood can be tested for the presence of heparin or similar antithrombogenic agents as Quick<sup>47c</sup> has, for example, demonstrated in the plasma after peptone shock.

On the basis that prothrombin, thromboplastin, calcium and fibrinogen are essential for the clotting of blood, and furthermore that coagula-

tion can be inhibited by the presence of natural anticoagulants such as heparin in plasma, a simple classification of hemorrhagic diseases (exclusive of those due to vascular disturbance) can be outlined. Absence or marked deficiency of any one of the primary factors gives rise to four potential classes of bleeding diseases, and a fifth type arises when a sudden liberation of heparin or a heparin-like substance occurs into the blood stream. An attempt will be made to group the common hemorrhagic diseases into these 5 classes. Although prothrombin and thromboplastin are treated as single substances, due cognizance is given to the possibility that these agents, like complement, may be made up of several components. If this be found, the classification would merely need to be enlarged, but not fundamentally altered.

1. **Diminished Prothrombin.** A. DEFICIENCY OF VITAMIN K. (a) *Dietary Origin.* In 1934 Dam and Schönheyder<sup>12</sup> in Denmark, and the next year Almquist and Stoekstad<sup>2a</sup> in this country demonstrated that a hemorrhagic disease could be produced in chicks fed a diet complete in all respects except for a new unknown factor, which was fat soluble. Dam named this new substance vitamin K. Almquist found that an ether extract of alfalfa had a high concentration of this vitamin and readily cured the bleeding dyscrasia in chicks. In 1936 Dam, Schönheyder and Tage-Hansen<sup>13</sup> found that they could not isolate prothrombin from the blood of chicks kept on a vitamin-K-poor diet, and Quick<sup>47c</sup> a few months later showed that the prothrombin began to diminish 4 days after removing vitamin K from the diet, and could be reduced to less than 10% of normal in less than 3 weeks. He further found that the prothrombin was promptly restored to normal by adding 2% alfalfa meal to the diet. These results definitely demonstrated that vitamin K is necessary for the synthesis of prothrombin in the chick. Recently, Greaves<sup>22</sup> succeeded in developing a hemorrhagic condition in rats solely by depriving the animal of vitamin K. The great majority of the rats, however, retained their prothrombin level even after prolonged deprivation of this food factor. It is well known as the result of Almquist's studies<sup>2b</sup> that vitamin K is synthesized by the bacteria in the intestinal tract, and this undoubtedly explains the difficulty of producing a hypoprothrombinemia by dietary means alone. It is therefore doubtful whether in the adult an inadequate diet by itself can ever affect the prothrombin concentration. There is reason to believe, however, that the hemorrhagic diathesis of the newborn may be caused purely by a lack of vitamin K and the disease therefore will be discussed under this heading.

*Hemorrhagic Disease of the Newborn.* It now appears to be quite certain that a deficiency of prothrombin is the cause of the hemorrhagic disease in the newborn. Brinkhous, Smith and Warner<sup>6a</sup> reported 1 case in which the prothrombin was extremely low, and recently Waddell, Guerry, Bray and Kelley<sup>65</sup> published 2 more cases in which the prothrombin likewise was greatly reduced. Since the latter 2 babies responded promptly to vitamin K administration, one can conclude that deficiency of this vitamin exists in certain babies. Brinkhous *et al.*, concluded that the prothrombin in newborn babies is normally less than 40% of the adult concentration, does not exceed this level up to the age of 2 weeks, and does not attain the normal level until at the end of the

first year. Their study is rather unsatisfactory since only 3 babies less than 11 days old (5, 8 and 8 days) are included in the series which they report. Quick and Grossman<sup>48</sup> were unable to confirm the findings of Brinkhous and his associates. On the contrary, they found that the prothrombin of babies 3 days or older was with few exceptions entirely normal. Furthermore, in babies 6 hours old, the prothrombin likewise was not greatly reduced. The values ranged from 70 to 80%. Surprisingly, however, in 2 out of 3 babies that were 1 day old, a very drastic reduction in the prothrombin was found, but this low level appeared to be of short duration since a prompt spontaneous rise occurs which in 1 or 2 days brings the prothrombin back to normal. These results have been confirmed by the Iowa investigators<sup>42</sup> with the use of Quick's prothrombin method. These findings greatly aid in understanding the nature of the hemorrhagic diathesis of the newborn. Apparently no reserve of prothrombin is built up in the fetus, and in 24 hours after birth this clotting factor may drop to a dangerously low level. Normally, a prompt spontaneous recovery of the prothrombin concentration occurs. If this is delayed, the typical hemorrhagic disease of the newborn develops. Vitamin K readily cures the disease. The source of the vitamin K which brings about the normal restoration of prothrombin remains to be found. As the baby consumes scarcely any food up to the time recovery is noted, an outside supply is improbable. Since vitamin K is synthesized by bacterial action within the intestine, it is logical to conclude that as soon as the baby takes water or food it infects the intestinal contents which at birth are sterile. With the establishment of an intestinal flora, the synthesis of vitamin K begins, and its absorption with the aid of bile ends the danger of bleeding. It seems not unlikely that the most important source of vitamin K in both infants and adults may be the products produced by bacteria within the upper intestinal tract.

(b) *Faulty Absorption.* It is well known that bile fistula dogs can develop spontaneous hemorrhage.<sup>26</sup> Hawkins and Brinkhous<sup>25</sup> found that the prothrombin was greatly diminished in these animals. More recently Greaves and Schmidt<sup>23</sup> showed that the prothrombin could be markedly lowered by either ligation of the bile duct or by making a biliary fistula. The prothrombin level in such rats could readily be elevated by either massive doses of vitamin K or by feeding bile salts. The suggestion of Quick<sup>47e</sup> that the absence of bile in the intestine leads to impaired absorption of vitamin K with a resultant lowering of plasma prothrombin is also the conclusion of subsequent workers.

It is highly improbable that a prothrombin deficiency can be produced in the adult by dietary means alone. Thus far a reduction of prothrombin has been observed only in biliary tract disease. Quick, Stanley-Brown and Baneroff in 1935<sup>50</sup> reported that in certain cases of jaundice a severe diminution of prothrombin was found. In 1938 these findings were corroborated by Brinkhous, Smith and Warner,<sup>6b</sup> and by Snell and others of the Mayo Clinic.<sup>59</sup> Both groups of investigators demonstrated the efficacy of treating this deficiency condition with vitamin K and bile salts. During the past year others<sup>11b,38,63</sup> have added cases of biliary disease including biliary fistula in which the hemorrhagic diathesis was successfully treated with bile and a vitamin K concentrate.

(c) *Sprue*. Engel<sup>17</sup> has reported that the hemorrhagic diathesis observed in sprue may be attributed to lack of vitamin K. It is highly probably that a low prothrombin concentration will also be found in various other conditions in which one may expect inadequate absorption of fat soluble vitamins. This conclusion has since the completion of this paper been clinically confirmed by Clark, Dixon, Butt and Snell.<sup>10</sup> They observed a deficiency of prothrombin in sprue, intestinal polyposis, chronic ulcerative colitis, gastrocolic fistula, and other conditions.

B. LIVER DAMAGE. A tendency to bleed often occurs in severe liver injury, and is frequently observed in acute yellow atrophy. In these conditions the fibrinogen is greatly diminished and it has been quite generally assumed that this accounted for the hemorrhagic condition. Recently Smith, Warner and Brinkhous<sup>58</sup> found that when a dog was subjected to prolonged chloroform anesthesia, a marked drop in prothrombin occurred which was far more abrupt and severe than the decrease in fibrinogen. Quick<sup>47</sup> likewise found that he was able by this means to reduce the prothrombin to less than 5% of normal. In view of these findings, it seems reasonable to postulate that in extensive parenchymatous damage of the liver, the cause of bleeding is the reduced concentration of prothrombin, and it seems safe to predict that further study will disclose that the blood in acute yellow atrophy is markedly deficient in prothrombin. Warner<sup>66</sup> was able to reduce the prothrombin level by partial hepatectomy, which further emphasizes the important rôle played by the liver. Warren and Rhoads<sup>68</sup> found that after total hepatectomy in the dog, a rapid decline occurred in the prothrombin of the plasma. These authors concluded from their results that the liver is essential for the formation of prothrombin.

The effect of liver damage on the prothrombin concentration of the blood is perhaps of greatest significance in the jaundiced patient. There are great variations in the response that patients with diminished prothrombin show to vitamin K therapy. A few react promptly and often even spectacularly while others respond sluggishly. Assuredly an adequate supply of vitamin K and good absorption are not the only factors. Utilization of this food accessory substance is equally important. It seems permissible to assume that the liver is concerned in converting vitamin K into the prothrombin component; consequently, if liver function is seriously impaired, the synthesis of prothrombin is decreased even though enough of the vitamin is consumed to fulfill adequately the normal metabolic demands. In other words, if impaired liver function occurs, more vitamin K is required to compensate for the faulty utilization. In the jaundiced patient, the diminished prothrombin may thus be due either to inadequate absorption or to faulty utilization; and perhaps in many cases both factors are present.

C. SWEET CLOVER DISEASE. Cattle which are fed sweet clover hay that has been spoiled are apt to develop a severe hemorrhagic disease which has considerable economic significance. Frequently simple operations such as castrating bull calves, and dehorning cattle, are followed by uncontrollable hemorrhage. Roderick<sup>54</sup> who was the first to investigate this disease thoroughly, observed that the prothrombin was decreased. This finding was confirmed by Quick,<sup>47c</sup> who studied the decrease of this clotting factor quantitatively. It is quite certain that

the sole coagulation defect in this disease is a severe reduction of the prothrombin of the blood, but how this is brought about is not known. Since the prothrombin is promptly restored as soon as the toxic hay is replaced by a normal diet, it seems rather improbable that any significant organic damage has occurred. It seems more likely that a toxic principle found in this hay directly inactivates the prothrombin. If this assumption is correct, one must recognize the possibility that similar toxic agents may perhaps be encountered clinically which may attack the prothrombin of the blood. At present, however, no human disease is known which resembles the condition produced by feeding toxic sweet clover to rabbits and cattle.

**2. Calcium Deficiency.** Although calcium plays an exceedingly important part in the coagulation mechanism, it is very doubtful whether even the extreme variations in its concentration which occur pathologically can influence the clotting time. *In vitro* experiments indicate that the concentration of calcium within a fairly wide range has no significant influence on the rate of coagulation. No hemorrhagic diathesis is associated with parathyroprivia although in this condition the calcium may reach the lowest concentration compatible with life. Ravdin, Riegel and Morrison<sup>52</sup> found that a patient in parathyroid tetany with a serum calcium of 4.6 mg. per 100 cc. had a normal coagulation time. At present, therefore, it is not possible to name any clinical or experimental bleeding condition that can be attributed to a deficiency of calcium. Nevertheless, much remains to be known. The influence of ionized and un-ionized calcium on the stability of platelets may perhaps be of much greater clinical importance than one would suspect.

**3. Thromboplastin Deficiency.** Thromboplastin appears to be widely distributed in the body as an intracellular substance, but only the fraction locked up in the platelet seems to be responsible for bringing about dysfunction of the coagulation process. In order for blood to clot, free or available thromboplastin is required. If there is no contamination of tissue juices, the only source is the platelet. An inadequate supply of thromboplastin obviously may arise in three ways: 1. Reduction in the number of platelets. 2. Platelets deficient in thromboplastin. 3. Abnormal resistance of platelets to lysis.

*A priori* it would seem that one can classify thrombocytopenia as a hemorrhagic disease on the basis of decreased thromboplastin. No doubt when prolonged coagulation in this disease is encountered, it may well be the result of thromboplastin deficiency. Howell<sup>27c</sup> has studied such a patient, who had a platelet count of 64,000 and also had a prolonged coagulation time. The platelet appears to have another function, a specific effect on capillary permeability, and in the purpuras this second function far overshadows the thromboplastin factor.

Apparently a marked reduction in platelets can occur without bringing about a delay in the clotting time. Interestingly a number of patients have been studied who may shift from a condition of hemophilia with a normal number of platelets but a delayed coagulation time to a purpuric syndrome with a marked thrombocytopenia but a normal clotting time. Such cases have been described by Pickering<sup>45</sup> and by Minot and Lee.<sup>36</sup> The information concerning the qualitative and quantitative variations of thromboplastin in the platelet is too conflicting and uncertain to be

of any specific value in differentiating and classifying hemorrhagic diseases. The importance of abnormal stability of platelets will be considered in the following section, "Hemophilia."

**A. HEMOPHILIA.** An adequate discussion of this subject would go well beyond the confines of this paper. An attempt will be made merely to show how much of the experimental evidence points to the possibility that in hemophilia the platelets are abnormally resistant and therefore yield thromboplastin too slowly to bring about coagulation within the normal time. The fact that hemophilic blood will always ultimately clot shows that no essential factor is absent.

What are the findings that suggest an inadequate quantity of thromboplastin? In 1908 Morawitz and Lossen<sup>37</sup> found that hemophilic blood clotted extraordinarily rapidly when an extract of kidney tissue was added. Kottmann and Lidsky<sup>30</sup> achieved the same rapid clotting with a liver extract. Schlossmann<sup>57</sup> and Mills<sup>35</sup> likewise demonstrated the effectiveness of tissue extracts. Since the tissue extracts of organs are almost always badly contaminated with prothrombin or thrombin, these earlier experiments were not entirely satisfactory. Quick, Stanley-Brown and Bancroft<sup>50</sup> succeeded in preparing a highly active preparation of thromboplastin from rabbit brain, which was free from prothrombin and thrombin. On adding a measured amount of this active material to hemophilic blood and to normal blood, both coagulated with equal rapidity. From these results Quick<sup>47a</sup> concluded: "This suggests that in hemophilia the prothrombin is normal in quantity and quality but thromboplastin is deficient."

Were prothrombin qualitatively altered, *i. e.*, less reactive as Addis and, more recently, Eagle<sup>14b</sup> have postulated, one would expect that the action of thromboplastin would not be as effective on hemophilic as on blood containing normal prothrombin. Howell<sup>27c</sup> in a recent comprehensive study on hemophilia has pointed out the probable error in the experimental studies of Addis and Eagle on which their conclusion is based. As the result of his latest studies, Howell concludes: "As far as blood is concerned we may conclude that one real difference between normal and hemophilic blood is that the latter contains less thromboplastin in its plasma. There may be other differences, but they have not been discovered. It would seem permissible to assume that this deficiency is sufficient to explain the prolonged clotting time of hemophilic blood."

Since thromboplastin takes on a new significance in the consideration of the basic defect in hemophilia, attention must be directed to the important source of this clotting factor, namely, to the platelet. Since the thromboplastin is locked up in the platelet and becomes available only after the latter disintegrates, the importance of the stability of these cellular elements is obvious. It seems that the environment rather than the platelet itself is the real determinant. Howell states that when platelets are removed from their natural environment, freed from plasma, and suspended in saline solution, they become exceedingly resistant, and do not break down when they come in contact with a foreign surface. Clearly this suggests that some factor in plasma governs the resistance of the platelet in plasma, and as a working hypothesis one might venture to suggest that this stabilizing influence is absent or depressed in hemo-

philia. In support of this is the finding of Govaerts and Grata<sup>21</sup> that platelets of hemophilic blood disintegrate normally in non-hemophilic plasma. Fonio,<sup>19</sup> however, found that washed normal platelets disintegrated as rapidly in hemophilic plasma, whereas the washed hemophilic platelets appeared more stable. More studies are required before one can definitely decide whether the abnormal stability of the platelet resides in the cell itself, or in its environment. It is fairly generally accepted, however, that the platelet is more resistant in hemophilia, and many investigators, particularly Sahli,<sup>56</sup> Wöhlisch,<sup>71a</sup> Minot and Lee,<sup>36</sup> Fonio,<sup>19</sup> Howell and Cekada,<sup>28</sup> and Opitz and Zweig<sup>41</sup> have furnished experimental evidence to support this conclusion.

It seems justifiable to classify hemophilia as a hemorrhagic disease caused by an insufficiently available supply of thromboplastin. No attempt will be made to discuss the important work of Patek and Stetson,<sup>43</sup> Pohle and Taylor,<sup>46</sup> Bendien and Van Creveld.<sup>5</sup> There is nothing in their findings which alters the general concept of hemophilia that has been presented.

**4. Fibrinogen Deficiency.** **A. ACQUIRED FIBRINOGENOPENIA.** The normal range of fibrinogen is roughly 0.2 to 0.4%, but may fluctuate beyond these limits. Since fibrinogen is essentially a passive agent in the coagulation process, its concentration within a wide range has no significant influence on the clotting time. Obviously, however, the density of the clot depends on the amount of fibrinogen in the blood, but even in this respect there is a wide margin of safety, for the fibrinogen may be greatly diminished, to as low as 0.02%, according to Risak,<sup>53</sup> without causing any evidence of a hemorrhagic tendency. As a matter of fact, a low fibrinogen with normal adhesiveness and clot retractive power is far superior hemostatically to a fibrinogen normal in amount but lacking these two essential properties. Nevertheless, a critical concentration must exist below which imperfect clot formation occurs, but no satisfactory determination of this level has been made.

Low fibrinogen may result from nutrition deficiency. Ham and Curtis<sup>24</sup> have shown that this may occur in pernicious anemia, scurvy and pellagra, thus confirming earlier work by Starlinger and Winands.<sup>61</sup> A marked fibrinogenopenia may be sometimes found in myelogenous leukemia, myelogenous sarcoma, and other diseases involving the blood forming organs.<sup>53</sup> Of great significance is the report by Jurgens and Trautwine<sup>29</sup> of a patient whose blood was completely incoagulable due to the absence of fibrinogen. On autopsy it was found that the liver was normal, but a widespread destruction of bone marrow had occurred due to metastasis from a prostatic carcinoma. Opitz and Silbermann<sup>40</sup> reported a similar case caused by generalized tuberculosis.

Low fibrinogen values are found in severe liver damage, especially in acute yellow atrophy. It is nevertheless doubtful whether the fibrinogenopenia is the actual cause of the bleeding which is frequently observed. As has already been stated, liver injury is usually followed by a drastic reduction of the prothrombin, and it seems certain that this latter factor is by far the more important in bringing about a hemorrhagic tendency. Smith, Warner and Brinkhous<sup>55</sup> showed that in dogs poisoned with chloroform, the prothrombin dropped more abruptly, to a greater degree, and for a longer period, than did the fibrinogen concentration.



Certain snake venoms such as that of the black snake of Australia and the tiger snake will clot fibrinogen *in vitro*, thus causing its complete disappearance from the blood.<sup>55</sup> This causes the incoagulability of the blood observed after a snake bite by these species. The hemorrhagic phase, however, is of short duration since fibrinogen again appears in the blood after several hours.

**B. CONGENITAL FIBRINOGENOPENIA.** Consistent and complete absence of fibrinogen from the blood due presumably to an inborn anabolic error has been reported only 3 times. Rabe and Salamon<sup>51</sup> described the first case in 1921, and the following year Opitz and Frei<sup>59</sup> published the second. Last year Macfarlane<sup>32</sup> presented a detailed case report of a third patient with congenital absence of fibrinogen. The first and third children were over 8 years old, indicating the importance of the vascular defense mechanism against hemorrhage, since in neither case was there any evidence that the blood was at any time coagulable. In the first patient, the platelets were normal in number but appeared resistant, whereas the third had a thrombocytopenia up to the age of 8. Macfarlane believes that the defect is inherited and has a recessive character. The parents of his patient were first cousins. Consanguinity of the paternal grandparents of their patient was reported by Rabe and Salamon.

It is interesting to note, but difficult to understand, that in spite of the complete incoagulability of the blood the 2 patients that lived to be 8 years of age seemed to have escaped serious incapacitating hemorrhages, such as bleeding into joints, more successfully than is usually the case in severe hemophilia.

The differential diagnosis between true hemophilia and fibrinogenopenia offers no difficulty. The simple addition of a few drops of thromboplastin solution such as is used in Smith's or Quick's prothrombin method will cause hemophilic blood to clot promptly, but will have no action on the second blood.

**5. Anticoagulants.** The presence in the blood of any agent which neutralizes or inactivates one of the four factors required for coagulation can hypothetically bring about a hemorrhagic state. The antithrombins and possibly the antiprothrombins, however, are the only ones which need to be considered clinically. There is no evidence that the blood ever contains any substance which renders fibrinogen incoagulable, or neutralizes thromboplastin. Likewise, the agents which prevent clotting by removing ionized calcium, such as the soluble oxalates and citrates, although very valuable for *in vitro* experiments are not encountered clinically as causes of hemorrhage. Except for the use of sodium citrate in transfusion, no extensive use of these reagents to inhibit coagulation *in vivo* is made at present.

In considering the antithrombins, it is important to recognize that blood contains a natural neutralizing agent of thrombin, which Quick<sup>47</sup> has shown to be either serum albumin itself or a substance closely associated with this protein fraction. Both fibrinogen and albumin have an affinity for thrombin, but the former is much greater. The fibrinogen-thrombin complex is very likely an intermediary step in the conversion of fibrinogen to fibrin. As soon as fibrin is formed, thrombin is reliberated to react with more fibrinogen, and only when coagulation is

complete does the albumin get a chance to combine and thereby neutralize thrombin. Quick has furthermore offered experimental evidence to show that heparin, which is *per se* not an antithrombin,<sup>47d</sup> acts by intensifying the antithrombin activity of serum albumin. By adding heparin to blood, a strong anticoagulant presumably an albumin-heparin complex is formed, which combines with thrombin before the latter can react with fibrinogen. It is entirely probable that this albumin-heparin complex likewise combines with prothrombin, thus preventing the formation of thrombin. Such a hypothesis will explain the recent findings of Brinkhous, Smith, Warner and Seegers<sup>7</sup> that heparin in conjunction with an unidentified substance of the plasma prevents the formation of thrombin. It is logical to speculate that this unknown factor is serum albumin. Due to the work of Best and his co-workers, heparin is now widely used to make blood less coagulable as a prophylaxis against thrombosis.

It is unlikely that heparin is present in normal blood. Quick<sup>47b</sup> has developed a titration method for detecting heparin in plasma, which is easily sensitive to less than 1 mg. of crude heparin per 100 cc. of blood. He was unable to find any trace of heparin in normal plasma. There is, however, good evidence that heparin or a closely related substance appears in the blood both in peptone and in anaphylactic shock. As the result of his studies, Howell<sup>27a</sup> attributed the incoagulability of the blood in peptone shock to heparin. Quick<sup>47c</sup> confirmed Howell's work and showed that the blood contained the equivalent of 1 mg. or more crude heparin per 100 cc. 5 minutes after the injection of peptone. Eagle, Johnston and Ravdin<sup>16</sup> demonstrated that anaphylactic shock was regularly associated with the presence of increased amounts of antithrombin in the blood. They did not attempt to correlate their findings with heparin. Earlier workers, particularly Pepper and Krumhaar<sup>44</sup> and Zunz and La Barre,<sup>72</sup> had likewise come to the conclusion that the antithrombin was responsible for the delayed clotting in anaphylactic shock. Recently Waters, Markowitz and Jaques<sup>69</sup> employing the finding of Chargaff and Olson<sup>9</sup> that protamine completely removes heparin from blood, were able to determine quantitatively the heparin in the blood after both peptone and anaphylactic shock. They further found that no antithrombin occurred in a shocked liverless dog, and concluded that this organ was responsible for the outpouring of heparin. Thus, the incoagulability of blood in the two experimental types of shock can be attributed to the sudden liberation of heparin into the blood. It seems justifiable to predict that if the blood of a patient in anaphylactic shock be analyzed it likewise will show the presence of heparin.

Many other substances are known which can inhibit the activity of thrombin. Of these, certain sulphur compounds such as cysteine, methionine, taurine and taurocholic acid, have been shown by Sterner and Medes<sup>62</sup> to act as anticoagulants. Earlier Carr and Foote<sup>8</sup> attributed the hemorrhagic tendency in jaundice to cysteine. With the advent of vitamin K, this hypothesis has been largely abandoned. It seems questionable whether these sulphur compounds or any other anticoagulants, save heparin, need to be considered as causes of hemorrhagic conditions encountered clinically.

Epitomizing the discussion of the hemorrhagic diseases caused by defects in the coagulation mechanism, the following outline for their classification is offered:

I. Diminished prothrombin (Prothrombinopenia).

A. Lack of vitamin K:

- (a) Dietary origin—absence of bacteria in intestines; (1) hemorrhagic disease of the newborn. (b) Faulty absorption—lack of bile salts; (1) obstructive jaundice; (2) biliary fistula; (3) sprue.

B. Liver damage—faulty utilization of vitamin K:

- (a) Post-anesthesia liver damage; (b) chloroform poisoning; (c) acute yellow atrophy.

C. Toxins:

- (a) Toxic sweet clover disease of cattle.

II. Changes in concentration of calcium in blood. (No clinical or experimental hemorrhagic conditions known which are attributable to changes of the calcium concentration.)

III. Deficiency of thromboplastin (Thromboplastinopenia).

A. Diminished number of platelets:

- (a) Thrombocytopenia (this disease is best classified under "defective vascular response" since the vascular dysfunction predominates).

B. Increased resistance of platelets:

- (a) Hemophilia.

IV. Decreased fibrinogen (Fibrinogenopenia).

A. Acquired fibrinogenopenia:

- (a) Nutritional deficiencies; (b) diseases of blood forming organs; (c) severe liver damage; (d) snake bites (Black snake of Australia).

B. Congenital.

V. Anticoagulants in the blood.

A. Liberation of heparin into the blood:

- (a) Peptone shock; (b) anaphylactic shock.

On the basis of this classification, a satisfactory diagnosis of a hemorrhagic disease can be made. A prolonged coagulation time by the Lee White method may be due to diminished prothrombin, thromboplastin, or the presence in the blood of an anticoagulant such as heparin. If the blood ultimately clots, the presence of fibrinogen is established. The concentration of prothrombin may be readily determined by one of the quantitative methods mentioned.<sup>49,67</sup> The presence of an anti-thrombin in the blood may be detected and even quantitatively estimated by the thrombin titration method.<sup>47c</sup> Hemophilia can be readily diagnosed, for the prothrombin will be found normal even though the clotting time may be exceedingly delayed. The clotting time of recalcified plasma, as employed by Baneroff, Stanley-Brown and Quick,<sup>3</sup> is particularly useful, especially with the recent modification proposed by Quick.<sup>47a</sup> The latter found that the clotting time of recalcified oxalated normal plasma was not very much influenced by the speed of centrifugation employed in obtaining the plasma. With hemophilic blood, however, the rate of centrifuging the blood so strikingly affected the clotting time that he has suggested using the procedure as a new

test for hemophilia. A quantitative determination of fibrinogen and of serum calcium completes the required investigation to determine a defect in the coagulation mechanism.

If no abnormality of the clotting process can be found, the hemorrhagic disease must be considered from the vascular point of view. Three tests are particularly useful: 1, The Duke bleeding time. 2, The capillary resistance test of Rumpel-Leede or Hess. 3, The clot retraction time. These tests are usually positive only in hemorrhagic diseases, such as the purpuras, in most of which the fundamental defect appears to be vascular.

**Summary.** A clinical classification of the hemorrhagic diseases is presented which is based on the coagulation theory of Morawitz. A disturbance of the coagulation mechanism can be brought about by diminished prothrombin, delayed liberation of thromboplastin, absence of fibrinogen, and the presence of antithrombins such as heparin in the blood. These defects are responsible for a large number of well known hemorrhagic diseases. The approach to the diagnosis of a hemorrhagic disease is very briefly indicated.

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## CARDIOSPASM OR ACHALASIA OF THE ESOPHAGUS.

THE terms cardiospasm and achalasia have been used generally to cover the same clinical picture, the differences in point of view on etiology accounting for the different names. Since there has been little agreement concerning the mechanisms and etiology of the condition, one finds a variety of terms, often based upon the etiologic concepts of the author, in the literature. These include idiopathic dilatation of the esophagus, phrenospasm, esophagectasia, hiatal esophagismus, megalo-esophagus, simple ectasia of the esophagus, and preventriculosis. In the present review the term cardiospasm will be used for the sake of simplicity and uniformity.

Since this term has been used rather loosely, even to include those patients with symptoms but without objective findings,<sup>6</sup> it may be well to make clear exactly what is meant by and included in the syndrome. Cardiospasm is the term used to include those patients who show dilatation and hypertrophy of the esophagus, together with a cardiac orifice which, at postmortem examination, is of normal size and without organic obstruction.<sup>49</sup> At postmortem examination the orifice permits the passage of a finger with ease, and water introduced into the esophagus at that time will run through the unnnarrowed orifice. In short, the cause of the obstruction is not active after death. In life,

diagnosis rests on the ability of the examiner to demonstrate non-organic obstruction at the cardiac sphincter.

First description of this disease has usually been accredited to Purton<sup>38</sup> in 1821. Recently it has been shown that it was described as far back as 1672, when Thomas Willis<sup>51</sup> reported a patient with the typical findings.

**Etiology.** Many possible explanations have been given for cardiospasm, particularly since the latter part of the 19th century. They fall naturally into two groups, those concerned with changes in the esophagus itself, and those accounting for the difficulty through the influence of adjacent organs and tissues. A great many of these are easily discarded because of striking incompatibilities with the physiologic and pathologic findings. For example, the dilatation present suggested that paralysis of the esophagus might underlie the changes. However, the hypertrophy of the walls, invariably present, surely indicates that activity is present, and indeed contractions may be seen with opaque media at roentgenoscopic examination. Lendrum<sup>29</sup> found in 13 cases no evidence of organic narrowing at the cardia, evidence against Mosher's theory of fibrosis of the terminal portion of the esophagus. Kinking was absent in all early cases with moderate dilatation, speaking against any prime importance of kinking as a mechanism of obstruction.

Extra-esophageal lesions as a cause of cardiospasm were suggested some 50 years ago when Handford,<sup>18</sup> in 1888, in reporting a patient showing cardiospasm together with hypertrophy of the heart and dilatation of the aorta, brought forward the possibility that compression between the aorta and the diaphragm was significant. This is obviously erroneous, but other theories related to extra-esophageal conditions have taken its place. All these will not be repeated here. At one time Mosher<sup>32a</sup> suggested from case studies that the passage of the esophagus past the surrounding liver tissue—the liver tunnel—might produce the clinical picture. Tissue studies have not confirmed this concept<sup>29</sup> and diseases producing hepatic enlargement do not obstruct the esophagus. Apparently Mosher has abandoned this theory, for his later reports<sup>32b</sup> suggest still other unconfirmed possibilities; such as fibrosis of the edges of the crura, peri-esophageal fibrosis in the crural canal, or fibrosis of the esophagus itself. Jackson<sup>23a</sup> has postulated that spasm of the diaphragmatic crura, or their failure to relax, compresses the esophagus, producing obstruction. Hill<sup>19</sup> also suggested a similar mechanism. He believed that no actual spasm of the crura occurred, but that incoördination took place in relaxation to let food through. The observation<sup>53</sup> of obstruction both above and below the diaphragm appears to rule out the possibility of phrenospasm as a cause of the clinical picture.

The term cardiospasm arose from the concept of von Mikulicz in the 19th century that the cardiac sphincter was in spasm. Despite difficulties in the demonstration of a true anatomic sphincter, this view has persisted up to the present time. As early as 1888 Einhorn<sup>10</sup> suggested another possibility concerning the cardiac sphincter. He described a patient in whom he could pass the stomach tube without resistance and concluded that the cardia probably failed to open reflexly during the act of swallowing. Kronecker and Meltzer<sup>26a</sup> had shown that nor-

mally the cardia easily opens with each act of swallowing. So the theory of the failure of the cardia to relax, or achalasia, had its beginnings. Again, in 1896, Rolleston made the same suggestion independently,<sup>21</sup> but it was not until the work of Hurst, 1913, that the theory received attention. Hurst introduced the term achalasia.

Early observations by Hurst<sup>21</sup> indicate that food normally travels down the esophagus, forced forward by a peristaltic wave. On reaching the cardia it pauses for a short while and then enters the stomach, apparently through active relaxation of the last inch or more of the esophagus, which acts as a functional sphincter. This sphincter receives a dual nerve supply, through the vagus nerve to Auerbach's plexuses and through the sympathetic nerve supply. It has been reported that no such supply exists,<sup>5,17,35</sup> and that definite responses occur.<sup>27,47</sup> The latter view appears to be acceptable.

If one accepts the above innervation of the cardiac sphincter, it has been pointed out<sup>21</sup> that four possible conditions suggest themselves as affecting the cardiac sphincter abnormally. 1, Overactive vagal influences would produce a patulous sphincter and a tonic esophagus. 2, Underactivity of the vagus would result in a lack of inhibition, so that, although not in spasm, the sphincter would fail to open for a bolus of food. This condition would be achalasia and no hypertrophy of the sphincter would be expected. Hypertrophy is found but rarely, and the inclusion of such cases is doubtful, as will be evident from remarks under "Diagnosis." 3, Sympathetic stimulation would cause true spasm of the sphincter; and 4, paralysis of the sympathetic fibers would permit unopposed vagus activity.

The authors point out that organic lesions would be responsible for the second and fourth conditions, while a nervous reflex would be more likely to account for the first and third. They further think it doubtful that cardiospasm ever occurs as a purely functional disorder in so-called nervous people, for in their experience hysterical dysphagia is due to a disturbance of a neuromuscular control of the voluntary part of the act of deglutition involving the upper esophagus and not the cardiac sphincter. Intermittency and not permanency of change would be expected with sympathetic stimulation.

Results of nerve section in animals have tended to confirm the above views. As far back as 1839<sup>10</sup> it was known that vagal section in rabbits caused stasis of food in the esophagus. Kronecker and Meltzer<sup>26b</sup> and others have shown similar results. More recently Knight<sup>25a</sup> has investigated the subject. He found that the type of response obtained from electrical stimulation of the extrinsic nerves to the thoracic esophagus appeared to depend on the nature of the muscle content. Results obtained from the lower portions of the esophagus showed the presence of an intrinsic sphincter mechanism with relaxation on vagal stimulation and contraction on sympathetic stimulation. Excision studies on nerves confirmed these findings and bilateral division of the vagi resulted in the clinical symptoms and Roentgen ray appearances of achalasia, the effect being permanent and increasing in severity as time went on. Subsequent sympathetic denervation of the cardia resulted in a complete cessation of symptoms and Roentgen ray evidence that food then entered the stomach. It was thus shown that the esophageal gets

a sympathetic innervation, and that there is a true cardiac sphincter. Section of these nerves confirmed Hurst's opinions on the human. Ferguson<sup>14</sup> obtained similar results on monkeys following vagotomy, with achalasia of the cardia.

From such studies, lesions of the vagus might be expected in patients. Patients are on record with vagal lesions<sup>37</sup> but in Lendrum's series 10 of 13 cases with adequate sections showed entirely normal vagus nerves. In 1924 Hurst suggested lesions of Auerbach's plexus and subsequently Rake<sup>39</sup> demonstrated such changes, with enlargement of the ganglia, cellular infiltration and later fibrosis, with scar formation and replacement and disappearance of the ganglion cells. All 11 cases up to the report of 1930<sup>21</sup> showed these changes. Some<sup>4,29,33</sup> have confirmed these findings while others<sup>15a</sup> have not. Lesions, of course, may be elsewhere in the vagus. Lendrum found in every one of his patients a striking or complete absence of ganglion cells in the plexus and demonstrated that the loss was equally great in the undistended portion of the lower esophagus, a factor against these changes being merely secondary to pressure.

Several causes, such as spread of inflammation from the esophageal lumen, syphilis, infective ganglionitis, primary vascular disease, congenital abiotrophy, and others have been suggested<sup>21</sup> but none has been accepted and the cause remains unknown. Furthermore, other bilateral lesions of the vagus, as already stated, could give rise to the same clinical picture. The disease has not escaped attempts to relate it to vitamin deficiency, for Etzel<sup>13</sup> has demonstrated destruction of the ganglia in vitamin B<sub>1</sub> deficiency. One would suspect, however, that vitamin B<sub>1</sub> deficiency would more likely be secondary than primary.

There is, therefore, considerable evidence to substantiate Hurst's views that a failure of the sphincter to relax is the cause of the esophageal retention. Reports on work with the weighted mercury bougie support this contention. Hurst found that such a tube may be dropped into the stomach through the esophagus in a patient with this clinical picture without resistance. If obstruction were due to spasm, resistance would be anticipated. At times he has found a tight gripping of the tube both on introduction and withdrawal, indicating actual spasm. This spasm has disappeared, however, with treatment of the esophagitis and has been ascribed to it.

The ease of inserting an instrument into the stomach with little evidence of spasm has been confirmed by some<sup>44,53</sup> and denied by others. Walton<sup>49</sup> states that a bougie passes the opening with great difficulty and is gripped firmly so that considerable force is required to withdraw it. There is, however, no hypertrophy of the sphincter as one might expect with spasm. The fact that two such authorities as Hurst and Walton disagree on such an important and apparently easily demonstrable point leaves one at a loss whether to accept the concept of spasm or of achalasia. Knight<sup>25c</sup> suggests that there may be two types of disease, one due to spasm, the other to achalasia. The Reviewer feels, however, that although this may be true it is quite strange that only patients with achalasia should seek out Hurst, and only those with spasm, Walton.



**Pathology.** Studies on the pathology of cardiospasm are few, due to the fact that the condition is uncommon and the treatment is effective. No attempt will be made to cover extensively the pathologic features. Early in the disease peristalsis presumably overcomes the resistance of the sphincter and prevents the development of symptoms.<sup>21</sup> When hypertrophy of the esophageal wall becomes inadequate to overcome this resistance, dilatation, accentuated by vagal paralysis, results. Peristaltic waves then would be ineffective, for they would not close the esophageal lumen to move the contents along. They would, however, cause further hypertrophy of the muscle. Food would accumulate in the esophagus until the column of food were sufficiently heavy to open the sphincter by gravity. Hurst's studies indicate that a column of food approximately 8 inches high is necessary. He states that when food is taken, nothing passes into the stomach at this stage until the contents of the esophagus are about 8 inches high, and then with further ingestion of food or fluid, the esophageal contents pass into the stomach until the food column is again 8 inches high, when the sphincter closes.

The marked dilatation of the esophagus has been described<sup>28</sup> as taking on three general forms—fusiform, which is the most common, flask-shaped, and sigmoid-shaped—the last probably being the terminal stage due to lengthening as well as dilatation of the esophagus. It is the rarest type. Dilatation becomes more marked than in any of the organic obstructions, due, at least in part, the adherents to the vagal paralysis theory believe, to reduced vagal tone. Hypertrophy has already been mentioned. Esophagitis is usual in the advanced stages of the disease when stagnation of food is constantly present. It, and ulceration, are considered secondary phenomena. Diverticula may form, and malignant degeneration sometimes occurs.<sup>24</sup> Hurst has found an associated hypertrophy of the salivary glands, especially the submaxillary, and this finding may be observed clinically. At postmortem the glands are normal except for their size, which probably results from overactivity.

Hypertrophy and dilatation end approximately an inch above the cardiac end of the esophagus. This terminal portion, the sphincter, is normal in size.

Other changes, such as those in Auerbach's plexus, have already been noted under "Etiology."

**Clinical Picture.** The disease may be well established before any symptoms develop. This has already been discussed, and is due, no doubt, to the ability of the esophageal musculature to overcome the obstruction. When hypertrophy fails to clear the esophagus, food accumulates and symptoms develop. At any rate, patients who have had very minimal dyspepsia<sup>23</sup> have come to autopsy with enormous thickening and dilatation of the esophagus in old age. Symptoms are not necessarily delayed, however, for the disease has been described in children in the first few days of life.<sup>2</sup>

The age of onset of symptoms varies widely, from infancy to extreme old age, but the disease is one usually of young adults. The average age has been reported as from 30 to over 50 years. In Walton's group, the average age when first seen was 52½ years. MacMillan<sup>30</sup> found the greatest incidence between 30 and 40. Lambert<sup>28</sup> gives the average

age as 40. Both males and females have been reported as being more frequently afflicted.<sup>46</sup> The disease is known to have lasted over 40 years.

The typical findings of cardiospasm need not be recapitulated here. There are three common important symptoms—difficulty in swallowing, regurgitation of food, and pain. Food seems to stop before entering the stomach. It seems to stick beneath the lower sternum. At first the dysphagia may occur only under emotional stress or with rapid eating, and may then be intermittent with periods of relief for day or weeks. Cold liquids are described as giving as much difficulty as solid foods. Warm liquids are swallowed more easily, but at times there are exceptions to this rule.<sup>46</sup> Solid foods sometimes are swallowed more easily than liquids.<sup>49</sup>

Difficulty in swallowing may not be very obvious. It may be accompanied by substernal pain which may be mild or extremely severe. If marked, as it is in about 25 % of the patients, it may overshadow difficulty in swallowing and lead to erroneous diagnoses, such as gall-bladder colic.

Pain of anginal type has been known to accompany cardiospasm. Verbrycke<sup>48</sup> reported 23 patients with some degree of aortitis, aneurysm, or angina, but a common etiology has not been brought to light. Attacks of pain on swallowing in patients with evidence of coronary disease and spasm of the cardia have been very similar to those of the angina of effort.<sup>9</sup> Dyspnea and attacks of suffocation are not unusual in the advanced stages.

At first regurgitation may be absent. Later the patient may regurgitate even before leaving the table. There is no nausea and the material raised is alkaline in reaction, and contains undigested food and mucus. This is not vomitus in the true sense for it does not come from the stomach. Eventually, as Walton points out,<sup>49</sup> regurgitation may occur spontaneously, or may be induced by taking a deep breath, by voluntary retching, or by tickling the fauces. It may then occur at varying periods following the meal, even during sleep, and may stain the patient's pillow or awaken him by regurgitation into the nose. Such a series of events has led to aspiration of food into the trachea and to the development of lung abscess.<sup>41</sup>

After the cardiospasm is well established, distress following meals, especially with fullness and discomfort, is common, and the patient may learn to regurgitate when the distress bothers him. Wasting may be extreme. The history may, therefore, simulate that of carcinoma of the stomach. Loss of weight is usually present and often reaches a certain level at which it remains constant.<sup>41</sup> Thus, symptoms may be atypical, and, in the absence of dysphagia in the history,<sup>23b</sup> the esophagus may not be suspected as the site of the lesion. Patients may have the impression of swallowing all right and still complain of vomiting.

The mode of onset of the clinical picture varies. Symptoms certainly do not always occur in the first stages of the disease. Mild at first, they may gradually develop and suddenly give way to acute difficulty with solid foods. This has been ascribed to sudden decompensation of the esophageal musculature. Sudden onset of symptoms is unusual, but does occur.<sup>12</sup> Freeman<sup>15b</sup> says the onset is usually

sudden, but most observers describe a gradual development of distress, at first with coarse foods, and later with more refined articles of diet. Acute flare-up of symptoms may be related by patients to emotional causes, financial worries, and the like,<sup>23b</sup> and a psychogenic theory has been developed.<sup>52</sup>

Cardiospasm has been described in association with a number of diseases. Heart disease has already been mentioned. Others are bronchiectasis, asthma, peptic ulcer, and diverticula. Bronchiectasis, pneumonia, and lung abscess may result from overflow from the esophagus during sleep,<sup>41</sup> although cardiospasm is not generally recognized as a cause of lung abscess. Sampson believes that in cases of unexplained pulmonary suppuration the esophagus should be studied routinely, in spite of the absence of symptoms referable to it.

**Diagnosis.** As a rule, cardiospasm gives little trouble in diagnosis. The clinical picture is usually characteristic and leads to confirmation by Roentgen ray studies, which, as a rule, suffice to clarify the problem. The appearance of the lower portion of the barium-filled esophagus, with a smooth tapering occlusion, is characteristic, and contrasts with the irregular appearance produced by carcinoma. Most clinicians feel that the recognition of the usual Roentgen ray findings is sufficient. However, Jackson<sup>23b</sup> believes that esophagoscopy is essential to confirm the Roentgen picture, for he has found carcinoma in patients reported by Roentgen ray examination as having cardiospasm. Freeman<sup>15b</sup> takes the usual point of view that, as a rule, Roentgen ray studies are adequate, but he believes there is a small group in which esophagoscopy is necessary.

Spasm of the cardia has been ascribed reflexly to carcinoma and ulcer of the stomach. It is also known that congenital pyloric stenosis may be accompanied by hypertrophy and dilatation extending above into the esophagus.<sup>22</sup> It is evident that, in the diagnosis of cardiospasm, disease below the cardiac sphincter must be ruled out.

Hysteria must be differentiated in young women. It tends to disappear as years go on. Cardiospasm does not.<sup>49</sup> The characteristic Roentgen ray picture is absent in hysteria. Other causes of dysphagia must also be considered. Walton states that he has seen esophageal dilatation comparable to that of cardiospasm in obstruction due to mediastinal tumor, but the obstruction was not at the diaphragmatic level. This degree of dilatation in organic obstruction is contrary to usual statements.

One condition which closely simulates cardiospasm is muscular hypertrophy of the cardiac sphincter, comparable to the pylorus in congenital hypertrophic pyloric stenosis. This disease is very rare, and the Roentgen features and symptoms may simulate closely those of cardiospasm. Obstruction persists after death.<sup>25c</sup>

In general, the differential diagnosis includes carcinoma and stricture of the cardia, congenital narrowing of the lower end of the esophagus, congenital hypertrophy of the cardia, para-esophageal hernia, esophageal diverticulum, angina pectoris, and the other disease states already enumerated.

**Treatment.** Drugs have been of no use. The most successful measure has been some form of dilatation of the cardiac end of the esophagus.

Since an ordinary bougie may be deflected from the cardiac orifice with danger of perforation, special procedures and bougies have been devised and have become standard forms of treatment. These include Hurst's mercury-weighted tube, hydrostatic dilators, use of the esophagoscope and a bougie, and digital dilatation through an opening in the stomach. All aim at an overdistention of the cardia to relieve the obstruction through injury to the circular muscle. Most popular are the methods of Hurst<sup>21</sup> and of Plummer,<sup>31,36</sup> the latter at times being modified to use air in place of water.<sup>15b</sup>

Details need not be given here. Plummer's method consists of the passage of a hydrostatic bag over a silk thread which has been slowly swallowed into the intestine until it may be held taut to guide the bag into the cardiac orifice. Then, hydrostatic dilatation of the silk covered bag is carried out. Until January, 1932, 810 patients with cardiospasm were observed at the Mayo Clinic.<sup>31</sup> Of these, 804 were dilated, and of 670 traced, 475 were considered cured, 105 moderately relieved, and 32 slightly relieved. Nine died of splitting of the esophagus. Thus, 71% of those receiving dilatation received complete relief. In most instances only one dilatation was required, but as high as 10 were given to some patients. This method has given good results in the hands of others as well,<sup>34,44</sup> and at times symptoms have been relieved without any appreciable change in the Roentgen appearance of the cardiac orifice.

Hurst's method utilizes a mercury weighted bougie. It is a flexible rubber tube filled with mercury to a sufficient weight to find its way through the cardiac orifice. It is first passed under fluoroscopic control in increasingly larger diameters (28 to 34 gauge) and, in Hurst's experience, has found little resistance. Patients then pass the largest tube themselves before meals, and leave it in place for 5 minutes. As symptoms warrant, the time and frequency of passage is reduced until it is passed in the morning only, then on alternate days, and finally once a week until discontinued altogether. Treatment is also directed toward the esophagitis. The patient is instructed to eat slowly, chew thoroughly, eat 4 meals a day, omit irritants from the diet, and to finish the meal with water or milk to wash the food into the stomach. The esophagus is emptied either voluntarily or by lavage after meals until the evidences of esophagitis have disappeared. All have not obtained the good results reported by Hurst,<sup>49</sup> and some have found in certain cases difficulty in passing the sphincter.<sup>25c</sup>

Artificial hyperpyrexia<sup>52</sup> and local diathermy<sup>3</sup> have been advocated. Generally, dilatation gives good results, but in certain instances fails. In these patients operative procedures have been used. These include plastic repair of the esophagus or stomach, and short circuiting procedures. One of the first operations was that of Mikulicz, which consisted of opening the stomach and dilatation of the cardia from below. Most procedures, however, are directed to eliminate the obstruction of the cardia. Their variety reflects in part the number of concepts of the cause of this condition. Gastrostomy alone is only palliative. Other procedures include an operation analogous to the Ramstedt procedure for pyloric stenosis. Other types of cardioplasty are designed to destroy the circular muscle and leave a large permanent opening. Invagination

of the esophagus, division of the vagi, and anastomoses between the esophagus and stomach have been tried. Certain degrees of success have been ascribed to practically all of these procedures.<sup>11,16,21,28,46,49,53</sup> Division of the vagi has aggravated the symptoms.

From the work of Knight<sup>25a,b</sup> one might expect that sympathetic denervation would be beneficial, and this has been true in some hands.<sup>1,7,11,45</sup> Craig and his associates first injected the ganglia with procaine and obtained relief before they attempted the operation. DeBakey<sup>8</sup> has carried out the same procedure with striking relief of symptoms and Roentgen ray evidence of passage of food without difficulty into the stomach. However, at short periods following actual section of the nerves, symptoms and signs of obstruction at the cardia returned.

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## PEDIATRICS

UNDER THE CHARGE OF  
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### THE USE OF SULPHANILAMIDE AND SULPHAPYRIDINE IN CHILDREN.

THE first drug of this group that was used as a therapeutic agent was prontosil. Domagk, who has been awarded the 1939 Nobel prize for this work, in 1935, observed the protective action of prontosil, a synthetic azo dye, on artificially produced streptococcic infection in mice. Similar results were also noted with a related compound which had the additional advantage of being more soluble. This became known as "prontosil soluble." Favorable observations were made on the action of these drugs in man, and they became the object of intensive study and research in Germany, France, England and the United States. The early interest in the drug was centered on its action against streptococcic infection. This organism has such great morbidity and mortality rates that an agent which would combat successfully the various manifestations of streptococcal infection is of the greatest importance. As soon as the drug was available commercially its use became widespread and often injudicious, so that along with reports of great benefit there began to appear mention of untoward and harmful results in its use. The early reports of its usefulness in streptococcal infection have, however, been justified and its use has spread to the treatment of other forms of infection.

According to Johnson,<sup>23</sup> some very interesting facts were brought out concerning the mode of action of these compounds. In the test tube or in contact with culture media containing viable organisms of known potency, the drug showed no bactericidal and only mild bacteriostatic activity. On the other hand, in the animal body the same organisms soon disappeared from the body fluids after administration of the drug. It was suggested that the curative action of the drug was due to a stimulation of the natural defenses of the body to such an extent that they were able to overcome the infection. Later it was shown that prontosil was reduced in the body with the formation of a compound which is known chemically as para-aminobenzenesulphonamide. This compound was given the non-proprietary name of sulphanilamide. It showed, but to a lesser degree than prontosil, the peculiar discrepancy between its *in vivo* and its *in vitro* effects.

The first applications of prontosil and of sulphanilamide were in the treatment of beta hemolytic streptococcal infections. Knowledge of its striking effect was especially impressed upon the public mind by the newspaper and radio stories of the beneficial effects of the drug in the severe streptococcal throat infection that threatened the life of a son of the President of the United States. Soon it was being used widely for streptococcal sore throat and other forms of streptococcal

infection. Hoyne and Bailey<sup>22</sup> gave an unfavorable report of its use in the treatment of streptococcic carriers. They found that, on the basis of the results observed by them, whatever value it may have in the treatment of acute streptococcic infections, it was not effective in the eradication of hemolytic streptococci from the noses and throats of scarlet fever patients at the end of a 4-week quarantine period.

Hickey<sup>16</sup> stated that in no branch of medicine had the effect of this new form of therapy been more effective than that in otolaryngology. This included such diseases as pharyngitis, nasopharyngitis, tonsillitis, peritonsillar abscess, cervical adenitis, otitis media, mastoiditis, otitic sepsis, streptococcic meningitis, ethmoiditis, orbital abscess and erysipelas. McLaurin<sup>30</sup> stated that the otolaryngologist would find that he could use sulphanilamide to advantage in treating patients suffering with the following conditions: 1, Pharyngitis, especially of the ulcerative streptococcal type; 2, sinusitis with purulent or seropurulent discharge; 3, rhinitis associated with a pharyngitis or sinusitis; 4, otitis media complicating a nasopharyngitis; 5, mastoiditis and cellulitis about mastoid wounds, especially when due to beta hemolytic streptococci; 6, purulent conjunctivitis associated with upper respiratory infections; 7, laryngitis or tracheobronchitis associated with an active pharyngitis; 8, Ludwig's angina; 9, furunculosis of the outer ear canal; 10, acute cellulitis with or without furuncle formation of the upper lip, columella, wings of the nose or floor of the nose, and 11, cavernous sinus thrombosis. Complications such as pneumonia of certain types and meningitis of otogenic origin or the result of sinus infections, formerly almost uniformly fatal, also responded to the use of the drug. He pointed out also the very important observation that children suffering from the acute infections enumerated seem to respond even more promptly to sulphanilamide than do adults, and they do not seem to be so definitely disturbed by the toxic effects of the drug.

Maybaum, Snyder and Coleman<sup>33</sup> were opposed to the indiscriminate administration of sulphanilamide for infections of the upper respiratory tract, many of which run a self-limited course. They claimed that the free use of the drug, aside from the dangers of toxicity, frequently obscures the clinical picture and often gave rise to a latent course of the disease. They felt that it was inadvisable to give the drug during the period of observation of a patient for a suspected mastoiditis, sinus thrombosis, petrositis and similar conditions because of the risk of masking the clinical picture and thus interfering with the diagnosis and surgical indications. In the same way Converse<sup>11</sup> remarked that the extraordinary success of sulphanilamide in the treatment of streptococcic otogenic meningitis had led to the widespread use of the drug in all cases of otitic infection in which the beta hemolytic streptococcus could be identified. While such enthusiasm for specific chemotherapy could be understood, he felt that the practice was open to criticism. He pointed out that the patient with meningitis was under hospital observation, and that treatment was continued until the spinal fluid had returned to normal. On the other hand, the patient with acute otitis media or mastoiditis received sulphanilamide only as long as there was persistent pain or discharge, and treatment was usually stopped on clinical instead of on laboratory evidence. Inadequate

sulphanilamide therapy has been followed by recurrence of otitic infections with beta hemolytic streptococci. The absence of the organisms should be proved by laboratory observations. The use of sulphanilamide in streptococcic ear diseases should be reserved for the treatment of infections that threaten life and it should not be used for the treatment of infections of minor severity. Inadequate treatment will result in recurrences and further spread of the infection. Hospitalization of patients receiving the drug is required not only because of the necessity of close laboratory observation, but because the amount of sulphanilamide required usually is so large that the danger of toxic manifestations demand close clinical observation. Woodward<sup>45</sup> agreed with the general opinion that sulphanilamide is particularly valuable in hemolytic streptococcic and certain types of pneumococcic infection. Since the majority of acute ear infections are due to these organisms, its routine use does affect the incidence of acute otitis media, the percentage ratio of operations to otitis media, the complications and results of treatment of acute ear infection.

Streptococcic meningitis is closely related to streptococcic otitis disease, and in fact it is often a consequence of the latter. Retan<sup>35</sup> observed that the advent of sulphanilamide had revolutionized the treatment of meningitis caused by *Streptococcus hemolyticus beta*. Formerly the disease had a mortality rate of 97 % but under the use of this drug it had been reduced to 20 %. Toomey and Kimball<sup>42</sup> felt that sulphanilamide was the therapy of choice in treating patients with beta hemolytic streptococcus meningitis, but they emphasized the importance of draining any localized area of infection by proper surgical procedures. They did not find it necessary to adopt the method of forcing fluids to produce increased perivascular spinal drainage in treating their patients. This is a hospital procedure and not easy to carry out in private practice. It was possible to secure a good concentration of the drug in the spinal fluid by simple ingestion. They first administer a massive initial dose of the drug followed at once by frequent maintaining doses. Along with this any focus of infection is removed surgically as soon as possible. They leave the hydrostatics of the spinal fluid alone unless the pressure is extremely high. As a result of this régime they found that, although sulphanilamide may prolong the life of a patient ill with a streptococcic meningitis, it would not give a complete cure if there was an untreated focus of infection. It will often immobilize the infection while the focus of infection is being localized.

Tixer<sup>41</sup> employed sulphanilamide with good success in the treatment of cerebrospinal meningitis of various origins. He found that the oral route of administration was the best under most conditions. The intraspinal administration may be necessary in extremely severe cases. He also used the drug as a preventive in epidemics of cerebrospinal meningitis by giving the drug to persons exposed to the infection.

According to Bucy<sup>9</sup> through an error in diagnosis a right cerebellar abscess was exposed with a bilateral suboccipital craniectomy. The contents of the abscess were aspirated and the surface of the cerebellum was contaminated with pus swarming with hemolytic streptococci, thus exposing the ventricular system and the subarachnoid space to this



infection. The abscess was not drained but the administration of sulphanilamide was begun at once. The patient improved steadily with almost no febrile reaction. At no time were there any signs of meningitis or of refilling of the abscess. This case suggested that all brain abscesses should be treated by trephining over the abscess, aspirating the pus and administering sulphanilamide. This conservative treatment might be all that was required, but if it did not clear the condition, radical treatment by drainage of the abscess could easily be done.

Another organism that has responded well to treatment with sulphanilamide is the gonococcus. Adler<sup>1</sup> used sulphanilamide in the treatment of 22 cases of gonorrheal vaginitis, 5 cases of gonorrheal urethritis in boys and 9 cases of gonorrheal conjunctivitis. In the latter, it was shown that the results are better with sulphanilamide than with any other form of treatment. In the boys' urethritis, 4 of the 5 cases gave prompt and definite response to the sulphanilamide therapy with cessation of discharge and with negative smears after an average of 2 days of treatment.

In an outbreak of gonorrheal ophthalmia in a home for infants and very young children, Newman<sup>34</sup> found that while improvement followed the use of local germicidal agents such as argyrol there was a marked tendency to relapse and the appearance of new cases in the contacts. Prompt improvement followed the initiation of sulphanilamide therapy with permanent disappearance of discharge and negative smears in 4 or 5 days.

Hoberg and Reck<sup>18</sup> studied the effect of sulphanilamide treatment of gonorrheal infections in 50 children. In their opinion sulphanilamide is justified in the treatment of gonorrheal infections in children. One advantage is its ease of administration without the psychic trauma that often results with irrigation treatments. In contradistinction to this, Holmes, Jones and Gildersleeve<sup>21</sup> reported that in 42 patients with gonorrheal vulvovaginitis treated with sulphanilamide by oral administration, 16 were relieved to the point of being able to return to school, having satisfied the Board of Health requirements of having three consecutive negative smears without vaginal discharge. Of these 16, 8 had recurrences of either positive smear or discharge in from 2 to 6 weeks. The failures did not seem to be due to inadequate dosage as the cases with high sulphanilamide blood serum concentrations showed as frequent failures as those with low levels of sulphanilamide. These discrepancies of results are difficult to explain. However, it may be that the important factor in permanent cure is not so much the high concentration of sulphanilamide in the blood at the beginning of treatment as it is the maintenance of an adequate dose for a period of time to insure complete eradication of the infection.

The use of sulphanilamide has become very popular in the treatment of urinary infections. One of the early advocates of this use of the drug was Helmholtz.<sup>14a</sup> In discussing the applicability of the various urinary antiseptics he stressed the necessity of the treatment being useful to any patient in any stage of the disease. He pointed out that methenamine in subacute and chronic infections of individuals whose urinary passages are normal is a very satisfactory drug, but that it

is of little use for patients who have acute infections, urinary stasis, or reduced renal function. This also applies to the ketogenic diet and mandelic acid, each of which is dependent for its action on a certain degree of acidity of the urine. With these latter two methods, it is necessary to control both the acidity and the concentration of the bactericidal substance. The use of sulphanilamide is much more simple. It can be given in the acute stage of the disease in addition to the usual forced intake of fluids and urinary alkalization. Although it acts best in an alkaline urine it acts also in acid urine and can be used in any phase of the disease. It gives very excellent results by oral administration but where the necessity arises it can be administered in the intravenous form.

In another contribution, Helmholtz<sup>14b</sup> emphasized that the diagnosis of urinary infection must include the type of infection, the state of urinary drainage and renal function as well as the presence of foci of infection in the urinary tract. Sulphanilamide has given the best results in the greatest number of conditions. In infections with *Strep. faecalis*, sulphanilamide has not proved successful and in this condition mandelic acid gives better results when the necessary acidity and concentration of the drug can be obtained.

Summerfeldt and Mitchell<sup>40</sup> studied 40 cases of urinary tract infection in children under treatment with sulphanilamide. Only 1 child manifested an intolerance. This patient had a cyanosis after the smallest doses of the drug. Although it has been customary to restrict the amount of fluids in administering sulphanilamide in adults for the purpose of securing better concentration of the drug, fluid restriction in children is not advocated because of the ease with which dehydration and acidosis develop especially in infants. For this reason the dosage of sulphanilamide in children has to be relatively higher than the doses given adults. In their series the authors found that urinary infections responded well to sulphanilamide therapy. *B. coli* infections respond readily to this treatment but *Strep. faecalis* infection is more resistant to this therapy.

Some success resulted from the treatment of pneumonia and pneumococcic infections with sulphanilamide. The results of treating this type of infection with the sulphanilamide derivative, sulphapyridine, have been so much more dramatic and successful that little space will be devoted to references of the use of sulphanilamide in pneumococcic infection. However, the results of any form of treatment in pneumococcic infection of the meninges have been so uniformly unsuccessful that record must be made of the fact that first with sulphanilamide some success against this type of infection was made. Hewell and Mitchell<sup>15</sup> reviewed the literature and found that 30 cases had been reported of recovery from pneumococcic meningitis. The treatment of these was in part the use of sulphanilamide or related compounds. They felt that it was reasonable to conclude that the sulphanilamide compounds were responsible for these recoveries in most instances, since the mortality was so high with other forms of treatment. Of the patients who received sulphanilamide and recovered, only 1 showed pneumococci in the blood culture. Negative blood cultures were reported in 16 patients and in 13 there were no blood cultures reported.

Of the 8 patients who received sulphanilamide and died, the blood cultures were positive for 7. This indicated that even with the use of sulphanilamide a blood stream infection with pneumococci is a factor in mortality and with such cases massive doses of sulphanilamide should be tried.

With such remarkable results following its use in a number of types of infection, it was only natural that the compound would be tried in many others, especially in those in which our treatment had been unsatisfactory. Experimental work by Kelson<sup>24</sup> on poliomyelitis in monkeys showed that there was no favorable reaction to the use of sulphanilamide in this disease. Hill and Goodwin<sup>17</sup> found that prontosil was effective in treating persons infected with *Plasmodium vivax* and with *Plasmodium falciparum*. This was especially true when the patients had had previous attacks. They remarked that the drug was more useful in the treatment of chronic and malignant infections and was not so useful in the treatment of benign and initial infections.

Of the 58 patients with rheumatic fever or chorea given sulphanilamide by Massell and Jones,<sup>32</sup> 31 (53%) showed toxic reactions. The chief manifestations were rash and fever. The rash was pink or red and usually maculopapular. It occurred on all parts of the body. There was slight, if any, itching associated with it. Occasionally the rectal temperature rose as high as 103° F. Fever frequently occurred unassociated with rash and then was usually higher than fever which accompanied rash. The toxic reactions occurred most frequently between the seventh and twelfth days after beginning the use of the drug. In 9 patients with toxic symptoms the repeated administration of the drug resulted in the development of a tolerance. Patients ill with rheumatic fever were particularly prone to the development of severe febrile reactions. This fact, together with the lack of any observed beneficial results, contraindicates the administration of sulphanilamide in the presence of acute rheumatic fever. The drug was given to 7 patients with slight to moderate chorea. In this condition there was no demonstrable improvement.

Anderson<sup>3</sup> treated 63 measles patients with sulphanilamide. At the same time a control group was under observation. It was found that the drug showed little effect in shortening the febrile period after admission to the hospital, but there was a slight reduction in the mean duration in the sulphanilamide-treated cases. The results did not suggest that this compound was of any great value in hastening the cure of the major complications of measles, but the duration of bronchopneumonia was materially shortened in the cases that had received sulphanilamide. Hogarth<sup>20</sup> found that routine administration of sulphanilamide by a fixed procedure of dosage gave a lower incidence of complications than those who did not receive such treatment. The results were not equally good with all complications, the incidence of enteritis being entirely unaffected by the drug. In regards to other complications, it would seem that there is some prophylactic value as the incidence of bronchopneumonia, otitis media and cervical adenitis was less than in the controls. The evidence showed that sulphanilamide was of value in reducing the incidence of complications due wholly or in part to secondary invasion by hemolytic streptococci, and the

best results were observed in pure streptococcic complications such as otitis media.

Wesselhoeft and Smith<sup>43</sup> found that sulphanilamide therapy in the eruptive stage of scarlet fever in the accepted dosage did not reduce the toxicity as manifested by intensity of the eruption nor the duration of the fever. The drug, given during the initial stage of the disease, did not reduce the incidence of complications. In cases in which the drug was continued longer the incidence was markedly decreased. It was not helpful in the complications involving the respiratory tract, but it was useful in certain infections of the mastoid cells. Infections of the blood stream and meningitis were found to be definite indications for the use of sulphanilamide. The carrier rate was not reduced by the use of the compound.

Stewart, Rourke and Allen<sup>39</sup> made a study on the excretion of sulphanilamide. They found that in man it was excreted almost entirely by the kidneys in either the free or in the conjugated form. The concentration of free and conjugated sulphanilamide in the blood resulting from a given per pound dosage was quite variable in different individuals; therefore it is important to have frequent determinations of blood level during intensive therapy with the drug. After sulphanilamide has been stopped the drug is rapidly eliminated from the body if renal function is normal and urine volume is adequate. It was found that the concentration of conjugated sulphanilamide in the blood was much lower than that of free sulphanilamide, but the rate of clearance of conjugated sulphanilamide was greater than that of free sulphanilamide. Because the precipitation of excreted sulphanilamide in urine at room temperature has been demonstrated, the possibility of stone formation in the urinary tract is emphasized if the urine volume should become too small during sulphanilamide therapy.

Stewart and Pratt<sup>38</sup> studied the effects of the drug on breast-fed babies as well as the excretion of the drug through the mothers' milk. Free sulphanilamide is excreted in human milk in concentrations closely corresponding to the values present in the blood stream. The concentration falls rapidly in the milk when oral administration is discontinued. It was found that breast-fed babies of full-time nursing mothers did show clinical evidence of toxic manifestations when the sulphanilamide was present in the breast milk in concentrations of 7 mg. per 100 cc. Traces of the drug were found in the blood of the baby and the urines of these babies contained amounts varying from 1 to 2.6 mg. per 100 cc. during a 24-hour period. However, a nursing baby cannot obtain an adequate therapeutic dose through the milk of a mother receiving an average clinical dose. Sulphanilamide has been found in the cord blood and in the amniotic fluid of women following the oral administration of 5 gr. of the drug every 4 hours throughout labor.

Following the widespread use of sulphanilamide many reports appeared giving toxic and untoward effects of the drug. Bigler and Werner<sup>4</sup> stated that cyanosis occurring during sulphanilamide administration has been reported frequently. It does not seem to depend on the age of the patient, the daily dosage or the length of time the drug is administered. The cyanosis usually disappears soon after the

withdrawal of the sulphanilamide, but it may not completely disappear for several days. It is questionable as to whether this manifestation is of any serious import. Changes in the blood picture are also seen after sulphanilamide administration. An example of this is the case of granulocytopenia reported by Alpert and Forbes.<sup>2</sup> The dosage in this case was comparatively small. Despite that a leukopenia with 100% lymphocytes developed, there was no complicating stomatitis and the patient recovered. Because the administration of nicotinic acid to patients suffering from pellagra or radiation sickness will ameliorate the symptoms and decrease or eliminate the excretion of abnormal porphyrin, McGinty, Lewis and Holtzclaw<sup>28</sup> studied the effects of this treatment on patients receiving sulphanilamide. The response of the patients to the additional administration of nicotinic acid was most gratifying. The unpleasant symptoms and the porphyrinuria were decreased. The most definite clinical change observed was a clearing of the mental apathy so often present with the ingestion of sulphanilamide.

Bigler and Haralambie<sup>6</sup> presented a very extensive review of the literature on sulphanilamide. Particular emphasis was laid on the range and limitation of application of the preparation and on what has been found to be the optimal dosage and mode of administration with the different diseases. Sulphanilamide has proved to be one of the most effective drugs in the treatment of certain diseases and they predicted many new derivatives and compounds of sulphanilamide. They defined the fields of usefulness of the drug and in their discussion of the toxicity and reactions of the drug they attempted to show not only its dangers but also its innocuousness when it is used intelligently.

McColl<sup>27</sup> remarked that the clinical success of sulphanilamide in infections with streptococci, gonococci and meningococci stimulated the search for new and related chemical compounds of therapeutic value. Of these numerous derivatives, 2-para-amino-benzene-sulphanilamide-pyridine has come forth as a valuable chemotherapeutic agent because of its effectiveness against pneumococci as well as the other organisms affected by sulphanilamide. Among the names which have been applied to this drug are sulphanilamidepyridine, sulphone-pyridine, pyridine sulphanilamide compound, daganan, M & B 693. The Council on Pharmacy and Chemistry finally named it "sulfapyridine." This is a slightly bitter powder which commercially is offered in tablets usually of 0.3 to 0.5 gm. McColl found it useful in pneumonia and also in a number of other infections, and it required a smaller dosage than did sulphanilamide. The toxic effects were less noticeable. Besides pneumonia he employed it in bronchopneumonia, osteomyelitis, meningitis, ruptured appendix, cellulitis of the hand and of the shoulder, impetigo neonatorum and epidermolysis bullosa.

According to McLeod,<sup>31</sup> nausea and vomiting are frequent accompaniments of the administration of sulphapyridine. These reactions are not related to the dosage of the drug or to the blood level. Since vomiting occurs in individuals to whom the drug has been administered parenterally, the effect would seem to be central, in addition to a possible local action on the stomach. Morbilliform skin rashes have been reported as well as numbness and tingling of the extremities.

Cyanosis due to methemoglobinemia occurs, particularly if high blood levels of the drug are attained. More serious toxic manifestations may appear involving the hemopoietic system and the urinary tract. Although there have been numerous reports of acute hemolytic anemia in patients receiving sulphanilamide, there has been little information available concerning blood destruction in patients receiving sulphapyridine. Hemolysis, when present, is due to the sulphapyridine itself and not to the pathologic process such as a pneumonia. Granulocytopenia also occurs with sulphapyridine.

Somers<sup>37</sup> treated 143 cases of cerebrospinal meningitis with sulphapyridine. These cases were all treated under adverse conditions in grass shelters with insufficient and unskilled nurses and the crudest care and food. The clinical condition of the patient and the cerebrospinal fluid were the criteria for the dosage of sulphapyridine injected. The youngest patients usually received proportionately the largest doses as they were the most seriously ill patients. Infants tolerated injections of 0.25 gm. in 40 cc. of distilled water intraperitoneally and 0.5 gm. intramuscularly. Saline suspensions were later used instead of the distilled water and resulted in less pain. In those receiving larger doses herpes of the lips were often observed. More rapid general improvement followed the intraperitoneal injections than the intramuscular injections. In most of the cases the cerebrospinal fluid became clear before the temperature fell to normal. Arthritis of the large joints and stiffness of the neck usually persisted for some days after the general condition had improved. While the usual case mortality of this disease in the Sudan is from 68 to 80 %, in the 143 cases observed in this report under treatment with sulphapyridine the case mortality was 10 %.

Hamilton and Neff<sup>13</sup> reported a case of influenzal meningitis, with the same organism in blood culture, that was treated with sulphapyridine. Under this drug the patient recovered simultaneously from the clinical and laboratory standpoint. The patient became afebrile on the sixteenth day.

According to Banks,<sup>4</sup> acute hemolytic streptococcal peritonitis, in which no focus in the abdominal cavity is demonstrable, is a rare and very fatal condition. The disease is essentially the same whether associated with scarlet fever or not, being probably always preceded by hemolytic streptococcic septicemia. The entire treatment of acute primary peritonitis has been revolutionized by the introduction of the new drugs. Both sulphanilamide and sulphapyridine have such potent action on hemolytic streptococci in the blood stream, in the meninges and as this case suggests in the peritoneum, that it may be thought justifiable and even desirable to refrain from laparotomy in view of the risks in desperately ill patients. Where there is a demonstrable primary focus in the abdomen this does not apply. In the case reported the child had scarlet fever plus a peritonitis and recovered under chemotherapy administration alone.

Brown<sup>8</sup> treated 27 cases of gonococcal vulvovaginitis with sulphapyridine, 31 with sulphanilamide and 6 with the sulphanilamide compound called uleron. All the patients treated were from 3 to 10 years of age. The duration of the period of treatment was cut down to only 4 days for the girls receiving sulphapyridine and to 10 days for those receiving

sulphanilamide. Perhaps the chief advantage found for sulphapyridine was that there was no necessity for local treatment except for merely swabbing the vulva with 1 part of acriflavine in 1000 parts of glycerin for the first few days. Improvement is apparent within a few hours in some cases treated with sulphapyridine and always within a few days with both sulphapyridine and sulphanilamide. The greater majority of the cases when once cleared remained clear even many months later.

While sulphapyridine has been used in these and other forms of infection, its action against pneumococcic infections have been particularly striking. Of pneumococcal meningitis Cable<sup>10</sup> said that it is rare, having been noted 39 times in 36,848 cases admitted to the Dudley Road Hospital in the past 3 years. The rarity of the condition is offset by its fatality rate, which has been usually accepted as 100%. His case was the first successful case reported in which sulphapyridine was used. Dunlop and Laurie<sup>12</sup> reported another successful result with the administration of sulphapyridine. Yule<sup>16</sup> reported a case that recovered under treatment with this drug. Pneumococcic meningitis followed mastoidectomy. McKeith and Oppenheimer<sup>29</sup> reported 5 consecutive recoveries under treatment with sulphapyridine, of which 2 recovered. This was a very great improvement in the mortality rate.

Discussing the treatment of pneumonia in children with type-specific horse and rabbit sera, Hodes *et al.*<sup>19</sup> stated that the results have been good and in some instances striking. However, this form of therapy has certain disadvantages when used in children because the type of pneumococcus must be determined before serum can be started and difficulties in typing may cause serious delay in starting therapy. In addition to this objection sometimes more than one type of pneumococcus is found in a patient and it is impossible to be certain which organism is causing the pneumonia. As a further objection serious serum reactions, while infrequent, do occur occasionally in spite of all precautions. Many of the patients are too young to be coöperative and are greatly disturbed by serum administration. The cost of the treatments is another important consideration. Although the mortality rate for pneumonia in children is very low, the condition is sufficiently serious to justify search for an effective therapeutic agent. The authors found that sulphapyridine was effective in primary pneumonia and also in the pneumonia accompanying measles and pertussis. As a rule, the administration of sulphapyridine was followed within 48 hours by a fall in temperature to normal and by prompt improvement and in 71 cases they had no deaths. They called attention to the possible ill-effects following the use of this drug such as hematuria, granulocytopenia and anemia. They emphasized the necessity of leukocyte counts, hemoglobin determinations and urine examinations at least every other day on all patients receiving the drug so that detection of the development of these untoward effects can be made as early as possible. Because these ill-effects are only temporary so far as is known, the withdrawal of the drug or reduction of the dosage is important.

Wilson *et al.*<sup>44</sup> attempted to determine the value of sulphapyridine in the treatment of pneumonia in infants and children, making no distinction between croupous pneumonia and bronchopneumonia. A control group was studied in parallel to the sulphapyridine group, observing such factors as age, severity of the pneumonia, the time at

which there was clinical improvement, significant fall in the temperature and clinical recovery. The case fatality rate is so low in pneumonia in children that this cannot be taken as a criterion of the efficacy of treatment. In their control and sulphapyridine groups there was no fatality. In all 70 cases with pneumonia were studied, half serving as a control group and half receiving sulphapyridine. The characteristics of the disease in the two groups were suitable for comparison of the results obtained. The administration of sulphanilamide apparently shortened the course of the pneumonia by approximately 3 or 4 days. By a statistical analysis it was demonstrated that the fall in temperature and the clinical recovery were significantly earlier in the sulphapyridine group than in the control group. As far as complications were concerned the number of cases under observation was too small to allow of evaluating the effect of sulphapyridine in this respect. The optimum dosage could not be determined but these observations indicated that a dosage which secures a level of free sulphapyridine in the blood of approximately 4 mg. per 100 cc. is therapeutically active. It was found that there were wide individual variations in the levels of free sulphapyridine so that frequent estimation of the blood concentrations are necessary. Vomiting and cyanosis were present in about half of the patients receiving sulphapyridine. In no instance was the cyanosis sufficient to cause concern. In the control group a number of the patients manifested cyanosis and vomiting in the acute stage of their pneumonia. Two patients on the drug had cutaneous eruptions but none of the severer reactions of the drug were observed.

Barnett *et al.*<sup>5</sup> studied the clinical results of sulphapyridine in 23 infants and children. In this group, 14 had pneumonia, 3 had empyema, 4 bronchitis, 3 pneumococcal peritonitis, 1 influenzal meningitis and 1 subacute bacterial endocarditis. They had results confirmatory of the reports concerning the use of the drug in adults. They suggested that in pneumonia if definite improvement did not result in 24 to 36 hours specific serum therapy should be used if the clinical conditions indicated its use and if the material was available. The toxic symptoms that were encountered following the use of this drug were mild nausea, vomiting and slight mental confusion, all of which usually subsided even with the continued administration of the drug. None of these manifestations were ever of sufficient severity to interfere with the use of the drug. Cyanosis due to the accumulation of methemoglobin was seen in most of the extensively treated cases but was readily controlled by the use of methylene blue.

Reynolds and Slobody<sup>36</sup> concluded that sulphapyridine when properly used in the treatment of the pneumonias of childhood brings about a precipitous fall in temperature, followed by a rapid disappearance of toxicity and a return of the respiratory rate and general condition to normal. They found that the signs of consolidation may persist for the usual length of time, but convalescence is markedly shortened and complications are rare. They commented on the relatively large doses of sulphapyridine required by children. This was directly proportional to the lack of age in the patients as infants under 2 years of age required a further 50% increase in the size of the dose on the basis of body weight to bring about results comparable with those obtained in older children.



Litteri, Litvak and Givan,<sup>26</sup> discussing the use of sulphapyridine in the treatment of pneumonia complicating pertussis, pointed out that vomiting, which is a predominating symptom of whooping cough, complicates the adequate administration of the drug. They found that the simple expedient of incorporating the drug in palatable vehicles was very useful. Sulphapyridine can be added not only to milk or fruit juices, but also to chocolate or malted milk. In addition, desserts such as mashed banana and cream, chocolate or rice pudding, and tapioca may be used. It has been found advantageous to vary the vehicle of administration. If emesis is at all prominent it is not possible to determine the amount of sulphapyridine actually ingested. In such cases the concentration of the drug in the blood must be observed by frequent blood studies necessitating frequent venipunctures. For several reasons this is not desirable, but especially in anemic and debilitated children. For this reason the authors have recommended rectal administration of sulphapyridine where pernicious vomiting interferes with the plan of dosage. They stress the need of larger doses than those given by mouth as the absorptive power of the rectum is less active.

Leopold and Sobel<sup>25</sup> treated 58 cases of lobar and bronchopneumonia in infants and children with sulphanilamide, with only 1 fatality. In 2 patients there was jaundice caused by toxic hepatitis. In 54 of the 58 cases the temperature fell to normal and the patient was apparently well 48 hours or less after administration of the drug had been started. In 49 cases this favorable result occurred within 36 hours, and in 35 cases within 24 hours. Compared to specific antipneumococcus serum therapy, sulphapyridine had a particular advantage in the treatment of the pneumonias of infancy and childhood, for it can be administered as soon as the diagnosis is made, thus avoiding the 1 day delay usually met in children before the pneumococci can be typed. Successful typing is often impossible in infants and children as was evidenced in the fact that only 14% of this series could be typed.

From a review of the literature it is found that the favorable reports on the use of the sulphanilamide group of preparations greatly predominate over the reports of untoward effects, blood dyscrasias and other sequelæ of its use. In fact, many of these are transient and clear up promptly after the use of the drug has been discontinued. Fatal complications have been the exception and deaths and serious after-effects are proportionately no greater, for instance, than those following the use of the arsphenamine preparations. Some disturbances in susceptible individuals should be expected in the use of any powerful chemotherapeutic agent. While its use is not recommended for indiscriminate application, especially in conditions of mild infections easily controlled by less powerful drugs, in severe infections the possibility of any complication or ill-effect need not be considered, as the primary requisite is the combating of the threatening infection. In the long run it will be found that the ill-effects from the drug are minimal after all.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER, 20, 1939

**Studies on the Detoxication of Local Anesthetics.** HELENE WASTL (Department of Anatomy and the Research Foundation, Hahnemann Medical College). Toxic doses of procaine hydrochloride and butyn sulphate were injected intramuscularly into guinea pigs and mice. It was observed that the signs of toxicity were delayed in onset and briefer in duration, and that the mortality incidence was decreased, when various calcium salts were injected simultaneously with the local anesthetics; this protective action was found to occur when the two substances were injected at separate sites as well as when they were injected after preliminary mixing.

The degree of protection provided by the calcium salts shows a direct logarithmic relationship with the size of the dose employed. The majority of the salts employed (the benzoate, levulinate, salicylate and lactate) are relatively less effective when injected separately than when they are injected after mixture, but this relationship is reversed in the

case of the gluconate. In all instances the protection provided against butyn sulphate is superior to that provided against procaine hydrochloride.

Neither the molecular weight of the calcium salt nor its hydrogen ion concentration plays a rôle in the degree of protection which it provides, but the degree of ionization appears to play a certain rôle when it is injected along with the local anesthetic. When injected after preliminary mixing, the salts, in order of decreasing effectiveness, rank as follows: benzoate, salicylate, levulinate, lactate, gluconate; when injected separately they rank (against procaine) benzoate, gluconate, salicylate, levulinate, lactate and (against butyn) benzoate, gluconate, levulinate, salicylate, lactate. As a practical clinical matter only two of these salts (the levulinate and the gluconate) are sufficiently non-irritant to permit of subcutaneous or intramuscular injection; of the two, as the above ranking demonstrates, the levulinate is to be preferred if it is to be injected as part of the anesthetic mixture.

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**The Effect of Insulin on the Electrical Activity of Nerve.** JOSEPH HUGHES (Institute of the Pennsylvania Hospital). The action of insulin on the after potentials of the cat's phrenic nerve has been studied. The nerves used in these experiments were mounted in a chamber through which was passing a mixture of 5% CO<sub>2</sub> and 95% O<sub>2</sub> according to Lehman's technique. The after potentials were recorded on a cathode ray tube.

After obtaining control pictures the nerve was then immersed in Krebs-Ringer solution containing zinc-free insulin. The pH of this solution was 7.4 to 7.45.

Solutions containing 0.002 of a clinical unit of zinc free insulin per cubic centimeter produced a change in the after potentials after 1 hour of soaking. This effect consisted in a shortening of the negative and deepening of the positive wave. The spike was usually unchanged. This effect has been observed with dilutions as great as 0.0002 clinical units per cubic centimeter. It is lost at higher dilutions. With dilutions of 0.2 clinical units per cubic centimeter undulating waves appear in the after potentials. These changes occur at a pH of 7.4. They were abolished by decreasing the pH to approximately 6.4 to 6.6 by means of increasing the CO<sub>2</sub> flow into the nerve chamber. Excitability curves, run after the insulin effect was established, showed that the irritability of the nerves paralleled the after potential changes. Nerves soaked in insulin which had been inactivated by mean of NaOH failed to show these after potential changes.

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**The Chemical and Physical Properties of the Gonadotrophic Hormone of Human Pregnancy Urine.** SAMUEL GURIN, CARL BACHMAN and D. WRIGHT WILSON (Departments of Physiological Chemistry and Obstetrics and Gynecology, University of Pennsylvania). Several fractionation methods have been employed for obtaining pregnancy urine gonadotrophic preparations assaying 4000 minimal effective doses (M.E.D.) per milligram when tested in the post-partum rabbit. The activity of these preparations could not be raised by further chemical manipulation. Analysis of such products indicates that they are glyco-proteins containing 50% carbon, 7% hydrogen, 12% nitrogen, 10 to 12% galactose and 5 to 6% hexosamine.

Upon examination in the Tiselius electrophoresis apparatus, a preparation containing 4000 M.E.D. per milligram showed a single mobile component with a mobility equal to  $4.85 \times 10^{-5} \text{ cm.}^2 \text{ sec.}^{-1} \text{ volt.}^{-1}$ . The substance was therefore essentially homogeneous with respect to electrical charge. The mobile protein, upon recovery, was biologically active and had the composition of a glycoprotein.

The same preparation likewise produced a single sedimenting band indicative of homogeneity when examined in the ultracentrifuge, as did a second preparation of similar biological activity prepared by a different method. The sedimentation constant ( $5 \times 10^{-13} \text{ cm. dynes}^{-1} \text{ sec.}^{-1}$ ) suggests a minimum molecular weight of 60,000 to 80,000 if the molecule is assumed to be spherical.

These observations indicate that hormone preparations containing 4000 M.E.D. per milligram are essentially pure.

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**The Functions of the Carotid and Aortic Bodies.** CARL F. SCHMIDT, J. H. COMROE, JR., R. D. DRIPPS, JR., and P. R. DUMKE (Laboratory of Pharmacology, University of Pennsylvania). Investigations in various laboratories (including this) show that the chemoreceptors of the carotid and aortic bodies are only a part of the mechanism by which the respiratory and circulatory responses to chemical changes in the blood are brought about. Their functions must therefore be ascertained by obtaining an adequate amount of valid quantitative data regarding their sensitivity and the size of their contribution to the total response. Investigations of the past 3 years, and still continuing, justify the following statements:

1. The impulses from the chemoreceptors are positively stimulant to the respiratory, vasomotor, and cardio-inhibitory centers; stimulant responses are not due to removal of an influence previously inhibitory, as in the case of the impulses from the pressoreceptors of the carotid sinus and aortic arch.

2. The thresholds of the carotid chemoreceptors to changes in  $\text{CO}_2$  tension and acidity are about 10 mm. Hg and pH 0.1 respectively, in lightly anesthetized, vagotomized dogs subjected to saline perfusion of both carotid bodies. The corresponding thresholds of the respiratory center, in animals similarly prepared, are of the order of 3 mm. and less than pH 0.02. The threshold of the chemoreceptors to anoxia is certainly lower than that of the center, if indeed the latter is stimulated at all.

3. Direct experiments on dogs have given no support to the contention of Heymans and Bouckaert (Ergeb. d. Physiol., 41, 28, 1939) that the carotid chemoreceptors are more sensitive and more rapid than the respiratory center in responding to changes in arterial  $\text{CO}_2$  tension. The same is true for the statement by Euler and Liljestrand (Skand. Arch. Physiol., 74, 101, 1936) that the chemoreceptors are continuously stimulated by the  $\text{CO}_2$  tension existing in arterial blood under resting conditions.

4. There is some tonic activity in the carotid bodies of some animals without anoxemia, hypercarbia, or acidosis, as shown by reflex respiratory depression on cooling the fluid perfusing the carotid bodies, but this occurs even when the fluid is greatly below the normal resting content with respect to any known chemoreceptor stimulant ( $\text{O}_2$  tension

over 150 mm., CO<sub>2</sub> below 1 mm., and pH 7.5). This may be due to the presence of receptors activated by temperature changes in the carotid bodies in such cases (Schmidt, Dumke, and Dripps: *Proc. Soc. Exp. Biol. and Med.*, 42, 31, 1939).

5. The conclusions derived from our previous studies (*Am. J. Physiol.*, 102, 94, 1932; 121, 75, 1938; 127, 76, 1939)—that chemoreceptor reflexes are less sensitive than the center to CO<sub>2</sub> and pH, that they constitute an accessory, supporting mechanism brought into play only in emergencies such as anoxemia, unusually great increases in CO<sub>2</sub> tension and acidity, or poisoning by drugs such as cyanide, lobeline, and so on—are therefore reaffirmed.

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**Influence of Organic Compounds Upon the Secretory Activity of the Frog Liver.** RUDOLF HÖBER and ELINOR MOORE (Department of Physiology, University of Pennsylvania). The ability of the isolated Ringer perfused frog liver, to concentrate dyestuffs in its secretion several hundred times, can be abolished entirely and reversibly by replacing in the Ringer solution about  $\frac{1}{2}$  of the NaCl by the isosmotic amount of a surface-inactive lipoid-insoluble hydrophilic non-electrolyte (disaccharide, hexose, pentose, polyhydric alcohol, amino acid, acid amide) or electrolyte (salts of lower fatty acids, hydroxyl carboxylic and dicarboxylic acids). This effect is not dependent upon changes in the perfusion rate. The opposite effect, promotion of secretory activity, can be brought about by polar-nonpolar electrolytes (salts of higher fatty acids, bile acids and other aromatic carboxylic acids, aromatic sulphonc acids) and surface-active non-electrolytes (alkaloids, digitonin, anesthetics). However, reversibility of this effect cannot be regularly observed, since cytolysis is frequently the end result. Suitable concentrations of inhibitory and promoting substances, simultaneously applied, counteract each other. Inhibitory and promoting substances, in general, exhibit opposite effects upon the dispersion of colloids (starch, lecithin, gelatin).

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ORIGINAL ARTICLES.

THE EFFECTS OF SULFANILAMIDE, NEOPRONTOSIL AND  
SULFAPYRIDINE UPON THE ERYTHROCYTE COUNT  
OF WHITE RATS.

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THE purpose of this paper is to present data on the relative effects of administration of equal doses of sulfanilamide (para-amino-benzene sulfonamide), neoprontosil (disodium-4-sulfamido-phenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3, 6-disulfonate) and sulfapyridine (2 para aminobenzene sulfonamido pyridine) upon the erythrocyte count of white rats. Data will also be presented on the body weight and intake of food and water of the animals which received these drugs.

Wien<sup>4</sup> reported the absence of anemia and porphyrinuria in two groups of 3 rats which received daily doses of sulfapyridine for 15 days; the doses used were 3 and 6 gm. per kg. of body weight respectively in each group. Sulfanilamide, however, when administered in daily doses of 1.5 gm. per kg. of body weight produced both a reduction in the erythrocyte count and an increase in the porphyrinuria. A daily administration of 4 gm. of sulfapyridine per kg. of body weight for 15 days produced a retardation in the growth of young rats which was comparable to that produced by giving daily 1 gm. of sulfanilamide per kg. of body weight. A daily dose of 1 gm. of sulfapyridine per kg. of body weight caused no significant inhibition of growth.

Rimington<sup>3</sup> reported an increased elimination of porphyrin in the urine of rats which had received sulfanilamide and prontosil (soluble). The presence of methemoglobin was demonstrated in the blood of these animals.

\* Commonwealth Fund Fellow from the University of Pennsylvania.

Kreutzmann and Carr<sup>1</sup> reported no change in the erythrocyte and leukocyte counts or in the concentration of hemoglobin of rabbits which received daily intramuscular injections of 0.25 gm. of prontosil for 21 days. An increase in the erythrocyte count, however, was noted following cessation of administration of the drug.

In a previous paper<sup>2</sup> we reported the details of a macrocytic anemia, the toxic symptoms observed and the gross pathologic findings in white rats to which sulfanilamide was administered in various doses for varying periods of time. It was found that adult rats which had received 2 gm. per kg. of body weight lost weight but that animals which received 1 gm. per kg. or smaller doses maintained their body weights very well. Enormously distended stomachs which contained retained food were found in the animals which lost weight. The decrease in the erythrocyte count which was observed was found to bear some relationship to the voluntary daily intake of water by the animals in so far as an increase in the consumption of water occurred and was maintained during a period at which the rate of decrease in the erythrocyte count was lessened.

In the experiments to be reported here, daily doses of each of the three drugs, sulfanilamide, neoprontosil and sulfapyridine, were administered separately to a group of 6 rats for a period of 4 weeks. The rats used were adult males of the Wistar strain; their average weight will be stated in the consideration of the results. The amount of each drug given was 1 gm. per kg. of body weight; each dose was made up to 6 cc. with tap water and was administered by means of a stomach tube. The rats were housed in single cages in groups of 3 and the amounts of food and water consumed were measured daily. The diet consisted of a commercial product which together with fresh water was provided *ad libitum*. Body weights were recorded periodically. The points on the various curves represent the average for the 6 rats of each group. Erythrocyte counts were made at weekly intervals by using samples of blood obtained by puncturing the ear. Platelet counts were made on the group of animals which received sulfapyridine; these counts were made at weekly intervals by the direct method of using a 0.3% solution of sodium citrate as the diluent.

**Results.** *Sulfanilamide.* The greatest and the most rapid decrease in the erythrocyte count occurred in the group of rats which received sulfanilamide. This decrease was most rapid during the first 2 weeks of the administration of the drug (Table 1), after which the curve depicting the changes in the number of erythrocytes tended to flatten out at the level reached at that time. The average amount of water consumed daily throughout the entire 4 weeks was greater than that during the control period. This increase, however, tended to be greater during the second 2 weeks at which time a further decrease in the erythrocyte count was in abeyance. The average initial body weight of this group was 294 gm. After

a transient decrease observed on the fourth day, which was accompanied by a decrease in the intake of food, the average body weight increased throughout the remainder of the experiment. This increase in body weight was not as great as that of a control group of animals, the latter group gaining an average of 7.2% in 1 month from an initial average weight of 298 gm. The increase in body weight of the group which received sulfanilamide was paralleled by an increase in the daily amounts of food consumed (Chart 1). This group of rats displayed marked cyanosis throughout the entire experiment.

TABLE 1.—EFFECT OF DRUGS ON TOTAL NUMBER OF ERYTHROCYTES OF WHITE RATS.

Drug.	Number of animals.	Dose of drug.	Total number of erythrocytes, millions per c.mm. of blood.				
			Control.	1 week.	2 weeks.	3 weeks.	4 weeks.
Sulfanilamide	6	1 gm. per kg.	9.83±0.12	8.70±0.20	6.95±0.24	7.36±0.13	6.48±0.13
Neoprontosil	6	1 gm. per kg.	10.67±0.14	9.78±0.19	9.62±0.25	8.48±0.16	8.78±0.26
Sulfapyridine	6	1 gm. per kg.	10.07±0.13	10.16±0.18	9.54±0.18	10.05±0.15	9.04±0.20
Controls	6	None	....	11.16±0.21	10.77±0.18	11.16±0.18	10.87±0.24

*Neoprontosil.* The average number of erythrocytes per cubic millimeter of blood of the animals which received neoprontosil also decreased during the experiment. This decrease, however, was less marked than that observed in the animals which had received sulfanilamide. Nevertheless, the decrease in the total number of erythrocytes in the blood of animals which received neoprontosil is significant statistically as is indicated by computing the differences and their errors between the control determinations and those of the test animals at the end of each week of administration of the drug (Table 1). The daily intake of food and water by the group which received neoprontosil showed no significant changes throughout the 4 weeks. The average body weight of this group of 6 animals before the administration of the drug was 370 gm. This average weight increased slightly during the first 11 days and then gradually decreased during the remainder of the 4 weeks until it was the same as the weight of the control animals (Chart 2). The control animals gained an average of 6% in weight in the same period of time. The animals that received neoprontosil also displayed cyanosis, but the cyanosis was in no instance as marked as that observed in the group of animals given sulfanilamide.

*Sulfapyridine.* The group of 6 animals which received sulfapyridine showed the least decrease in the total number of erythrocytes and the slight decrease which was observed was not constantly maintained. At the end of one week there was no change in the



erythrocyte count, but at the end of the second week the mean number of erythrocytes was below that observed during the control period. At the end of the third week the average erythrocyte count had returned to the control level, but at the end of the fourth week it had decreased 10% below the control values. When the data were appraised statistically and the differences together with their errors computed, no significant effect was shown to have been produced until the end of the fourth week. The differences between the mean control value ( $10.07 \pm 0.13$ ) and that attained at the end of the fourth week ( $9.04 \pm 0.20$ ) was  $1.03 \pm 0.24$ . This difference, although not large, is statistically significant and the conclusion is thereby indicated that sulfapyridine had induced a slight but real

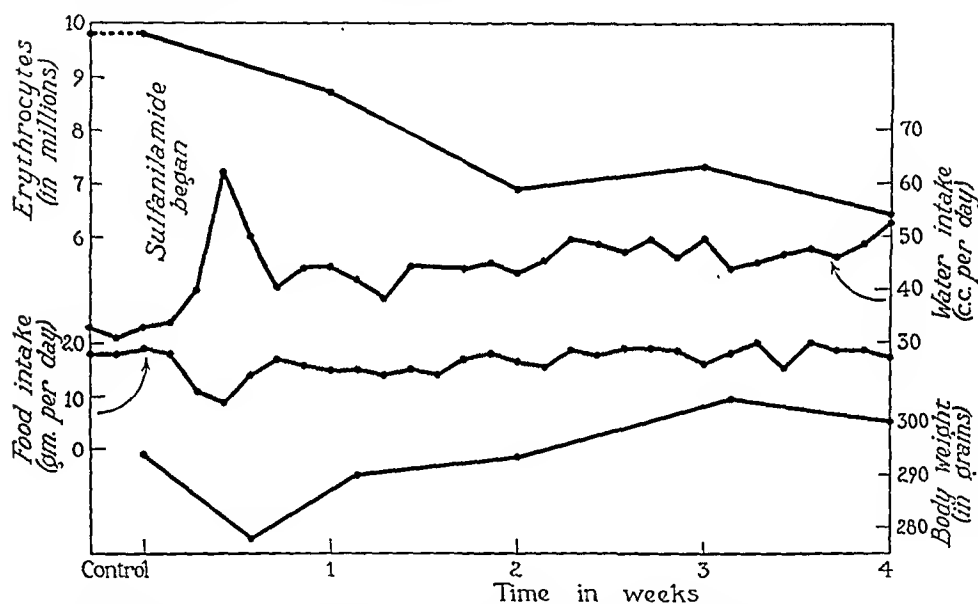


CHART 1.—Trends in the erythrocyte count, body weight and daily intake of food and water of 6 animals which received 1 gm. of sulfanilamide per kg. of body weight daily for a period of 4 weeks.

anemia (Table 1). Erythrocyte counts made at the end of the fifth and sixth weeks upon these same animals, which continued to receive the daily amounts of the drug, remained essentially the same as they did at the fourth week ( $9.12 \pm 0.15$  and  $9.11 \pm 0.37$  respectively), but data assembled at the end of the seventh week showed a mean erythrocyte count of  $9.67 \pm 0.27$  million per c.mm. of blood. This figure is not significantly different from the established control values and must indicate that the slight anemia induced by the drug during the fourth, fifth and sixth weeks was but transient. Administration of sulfapyridine was discontinued after the seventh week and sulfanilamide in similar doses was substituted. Within 1 week after the animals had been on sulfanilamide the erythrocyte count decreased to 25% and within 2 weeks to 35% of the orig-

inal value. Platelet counts made at weekly intervals during the first 4 weeks of the administration of sulfapyridine revealed no significant changes. The average platelet counts of 6 animals at weekly intervals were 823,000 (control), 750,000, 830,000, 746,000 and 730,000 per c.mm.

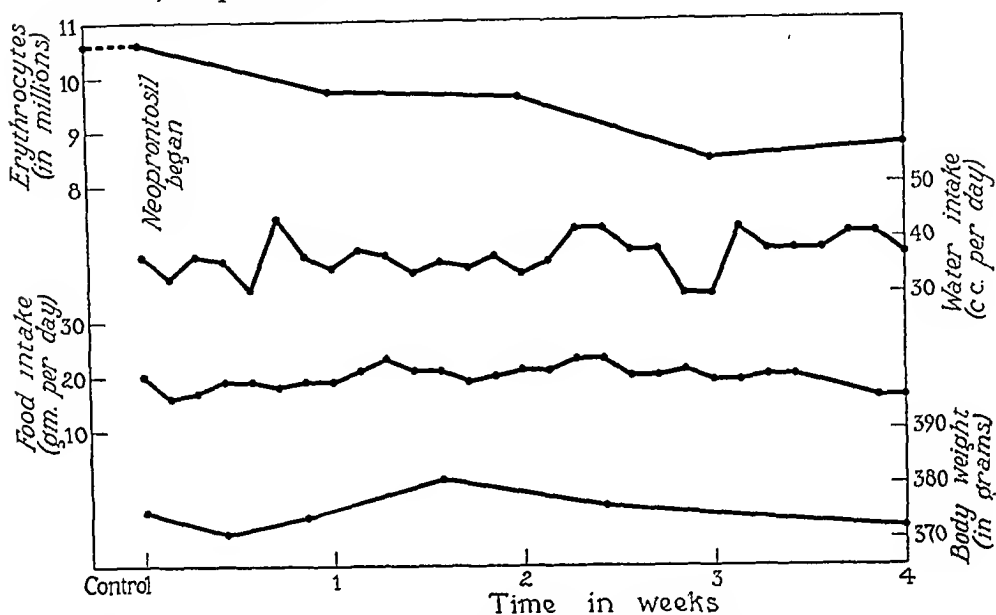


CHART 2.—Trends in the erythrocyte count, body weight and daily intake of food and water of 6 animals which received 1 gm. of neoprontosil per kg. of body weight daily for a period of 4 weeks.

The initial average body weight of the 6 animals which received sulfapyridine was 300 gm. This decreased to 290 gm. on the fourth day of the experiment and thereafter it varied between 290 and 295 gm. for the remainder of the 7 weeks during which the drug was administered. The average initial body weight of control animals increased 7.2% by the end of the fourth week. There was no significant change in the daily intake of food or water (Chart 3). During the entire 7 weeks cyanosis was not detectable in the group of animals which received sulfapyridine, however, when sulfanilamide was substituted for the sulfapyridine, intense cyanosis soon developed and was maintained.

**Comment.** The administration of the three drugs in the same amounts daily and by the same route afforded an excellent opportunity to study the effects of these drugs on the erythrocyte count and to observe any possible toxic manifestations which might have occurred. With respect to the erythrocyte count, the results indicate that sulfanilamide depressed the count the most and sulfapyridine the least, while the effects induced by neoprontosil were somewhat in between those produced by the two drugs (Chart 4). Cyanosis was rather intense in the group of animals which received sulfanilamide but was less intense in the animals which received

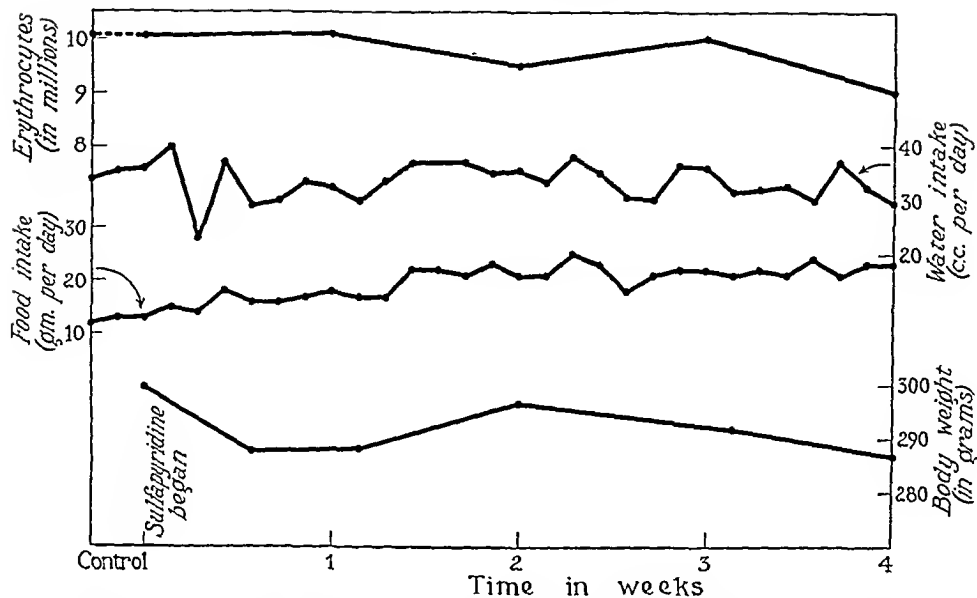


FIG. 3.—Trends in the erythrocyte count, body weight and daily intake of food and water intake of 6 animals which received 1 gm. of sulfapyridine per kg. of body weight daily for a period of 4 weeks.

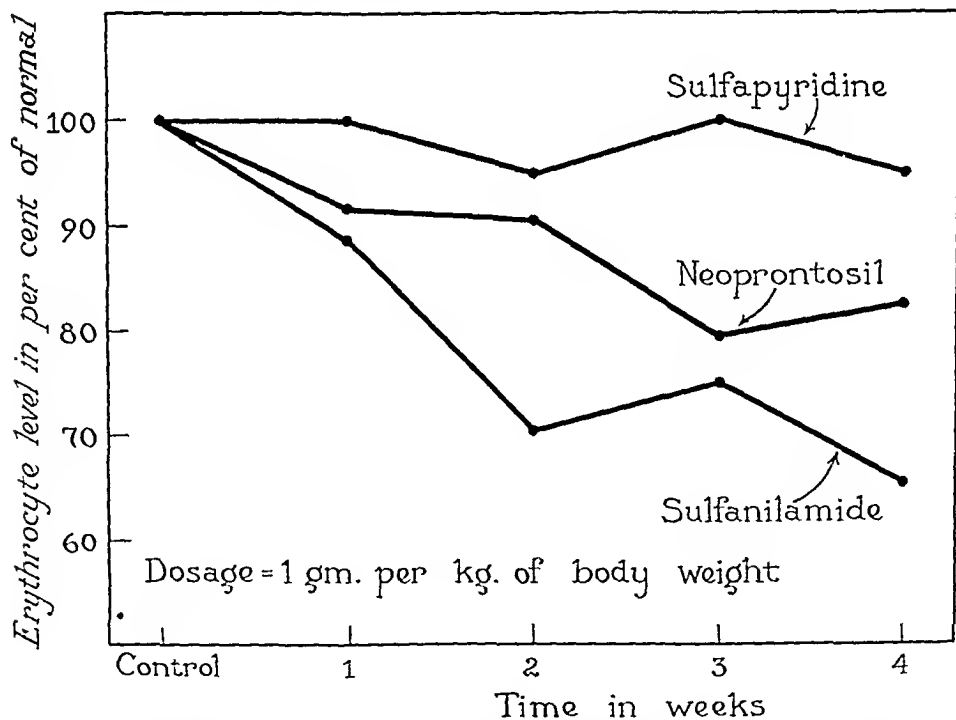


CHART 4.—Comparison of effects of equal doses of sulfapyridine, neoprontosil and sulfanilamide upon the erythrocyte count of rats. The points on the curves represent the erythrocyte counts at the weekly intervals; the erythrocyte counts are expressed as per cent of the normal count.

neoprontosil. Clinical cyanosis was not detectable in the animals which received sulfapyridine. The animals which were used in these experiments were adults, hence satisfactory comparison cannot be made with the results obtained by Wien who used young rats. In our experiments, the animals which received neoprontosil and sulfapyridine failed to gain weight, while controls in the same initial weight ranges did gain. The animals which received sulfanilamide gained slightly in average body weight but not as much as the controls. We have observed loss of body weight in rats which received larger doses of sulfanilamide, including the dose used by Wien (1.5 gm. per kg. of body weight). Convulsions and distended stomachs, the occurrence of which we have already reported in cases in which animals received sulfanilamide in large doses, were not observed in the animals which received sulfapyridine or neoprontosil.

**Conclusions.** 1. When sulfanilamide, neoprontosil and sulfapyridine were administered in equal doses by the same route, sulfanilamide produced a greater reduction in the total number of erythrocytes than did neoprontosil, which in turn was more potent than sulfapyridine in reducing the red cell count.

2. Cyanosis was more intense in the animals which received sulfanilamide than it was in the group which received neoprontosil; clinical cyanosis was not detected in the animals which received sulfapyridine.

3. All three groups of animals failed to gain in body weight, as compared with controls observed during the 4 weeks of the experiment.

The authors are indebted to Dr. Alfred Uihlein for the platelet counts cited.

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### NUTRITIONAL MICROCYTIC HYPOCHROMIC ANEMIA IN DOGS CURED WITH CRYSTALLINE FACTOR I.

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PUPPIES maintained on a purified casein diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B<sub>6</sub>) developed severe microcytic hypochromic anemia.<sup>3</sup> They also failed to grow

properly and 3 of 4 animals exhibited generalized convulsions. Addition to the diet of a concentrate prepared from rice bran and containing Factor I cured the anemia, but in one animal, in spite of this the convulsions continued. Chick, Macrae, Martin and Martin<sup>1</sup> reported similar findings in young pigs. Feeding of their liver eluate which contained Factor I was followed by resumption of growth, cure of anemia, and disappearance of convulsions.

These findings did not justify the conclusion that the material in rice bran extract and liver eluate which cures rat dermatitis is identical with the substance that cures anemia in puppies and pigs. The purpose of this paper was to ascertain by use of crystalline Factor I whether they are the same. A preliminary report of these observations has been made.<sup>2</sup>

**Materials and Methods.** Three adult mongrel dogs were fed unrestricted amounts of the synthetic casein diet<sup>3</sup> supplemented daily with 0.05 mg. of thiamine hydrochloride per kilo, 60 micrograms crystalline riboflavin per kilo, 4 cc. per kilo of a liver extract containing Factor II (chick antidermatitis factor) and nicotinic acid but free from Factor I, and halibut liver oil. Dog 2 received in addition 15 mg. of nicotinic acid daily. Supplements were not incorporated in the diet but administered separately. Crystalline Factor I prepared by method of Lepkovsky<sup>4</sup> was used in the studies.

**Results.** Dog 1 weighed 6.2 kilos when started on the synthetic diet. There was a steady decrease in red blood cell count and hemoglobin after the 22d day of the diet. By the 120th day the red blood cell count had decreased from 8.68 million to 5.16 million per c.mm., hemoglobin from 14.7 to 7.5 gm., hematocrit from 62 cc. to 25 cc. and mean corpuscular volume from 71.4 to 48.4 cubic micra. The dog appeared normal except that she was quieter than usual. Serum-iron on the 113th day was 0.476 mg. per 100 cc.\* Oral administration of 60 micrograms of crystalline Factor I per kilo was started on the 127th day when the red blood cell count was 4.52 million, hemoglobin 6.2 gm., and reticulocytes 1.8%; weight was 6.4 kilos. This addition to the supplements was followed by reticulocyte rise to 14% (third day of therapy) and rapid rise in red blood cells and hemoglobin. The weight which had been approximately stationary increased rapidly. Twenty-one days after starting Factor I administration, the red blood cell count was 7.09 million, hemoglobin 14.5 gm., hematocrit 44 cc., mean corpuscular volume 62.1 cubic micra, and weight 8.1 kilos.

The anemia of Dog 2 which developed while on the synthetic diet did not respond to daily oral administration of 0.5 gm. of iron and ammonium citrate and 0.5 mg. copper sulphate. The response of red blood cell count, hemoglobin, and weight to the oral administration of crystalline Factor I was prompt (Table 1). Factor I was

\* Blood for serum-iron determinations was collected in iron-free paraffined centrifuge tubes, centrifuged at once and the supernatant serum transferred to glass-stoppered flasks which were mailed to St. Louis where the serum-iron determinations were made. The authors wish to thank Dr. Carl V. Moore for these determinations.

TABLE 1.—RESPONSE OF WEIGHT, RED BLOOD CELL COUNT, HEMOGLOBIN, RETICULOCYTES, HEMATOCRIT, AND WHITE BLOOD CELL COUNT OF DOG 2 TO DIET DEFICIENT IN FACTOR I AND SUBSEQUENT RESPONSE TO CRYSTALLINE FACTOR I.

Day.	Wt. in kilos.	RBC, million per c.mm.	Hgb., gm.	WBC.	Retic., %.	Hem., cc.	MCV.	Remarks.
0	8.1	6.88	12.3	14,700				
6	8.4	6.77	10.8	7,250				
26	8.9	8.11	11.5	9,450				
40	9.1	6.83	11.7	12,200				
54	9.0	7.39	10.2	9,900				
68	9.0	5.47	8.3	7,700				
76	8.8	5.25	8.4	9,100	0.0	31.0	59.0	
78	...	5.25	7.2	10,500	0.4			
83	...	4.61	7.6	11,100	0.0			
84	...	...	...	...	0.4			
85	...	...	...	...	0.0			
86	8.8	5.21	7.0	...	0.0			
87	...	...	...	...	0.0			
88	...	...	...	...	0.0			
89	...	...	...	...	0.0			
90	8.5	4.54	7.0	15,350	0.2	...	...	Scrum-iron 0.356 mg. per 100 cc.
91	...	...	...	...	0.8			
92	...	...	...	...	1.8			
93	8.5	4.46	6.6	11,500	1.5			
94	...	...	...	...	1.4			
95	...	...	...	...	0.6			
96	...	...	...	...	1.2			
97	...	4.14	6.5	11,700	1.2	24.0	57.9	
98	8.4	...	...	...	1.2	...	...	0.5 gm. iron and ammonium citrate and 0.5 mg. copper sulphate daily.
99	...	...	...	...	2.4			
100	8.3	4.20	6.7	9,250	1.4			
101	...	...	...	...	1.9			
102	...	...	...	...	1.7			
103	...	...	...	...	2.1			
104	8.3	4.15	5.8	8,000	0.8			
105	...	...	...	...	0.8			
106	...	...	...	...	0.8			
107	8.3	3.64	4.8	11,000	2.3	20.0	54.5	
108	...	4.18	4.5	...	2.5			
109	...	...	...	...	3.5			
110	8.1	3.54	4.8	5,400	2.3	...	...	60 micrograms crystalline Factor I per kilo daily.
111	...	3.72	5.0	4,800	4.6			
112	...	4.16	5.3	6,300	12.0			
113	...	4.53	6.2	5,750	12.8			
114	...	4.86	6.9	7,350	11.5			
115	8.3	4.53	7.2	3,300	9.6			
116	...	...	...	...	10.0			
117	...	...	...	...	5.2			
118	...	4.28	9.2	3,750	4.8			
119	...	5.32	9.2	4,200	2.8			
120	8.5	6.01	10.8	3,800	5.0	35.0	58.2	
125	...	5.01	10.9	3,000	1.3			
129	9.0	5.47	11.2	4,200	1.6			
133	9.1	6.46	14.2	5,700	...	43.0	66.6	
140	...	7.14	14.5	6,950	...			
141	9.7	...	...	...	...			Factor I discontinued.
148	9.5	7.04	15.4	11,800	...	45.0	63.9	
176	9.1	6.42	15.4	8,500	...			
190	9.2	5.06	10.1	7,650	...			
207	8.6	5.16	9.4	5,750	...	27.0	52.3	
218	8.2	4.46	7.3	7,600	0.6			
221	8.2	3.02	5.9	...	0.0			
222	...	3.12	6.1	...	1.0			
223	...	...	...	...	1.0			
224	...	3.88	7.0	...	3.0			
225	8.0	3.82	8.1	...	4.4	22.0	56.5	
226	...	...	...	...	2.4			
227	...	3.89	6.4	6,900	2.7			
228	7.9	4.02	6.6	...	2.0			
229	...	3.92	5.7	...	1.2			
230	...	...	...	...	1.2			
231	...	3.46	4.8	5,050	1.2			
233	7.8	3.45	4.8	6,250	1.6	17.0	48.9	60 micrograms crystalline Factor I intravenously, daily.
234	...	3.86	6.5	...	8.4			
235	8.0	4.05	6.4	...	6.6	20.5	50.6	
236	...	3.56	5.5	7,900	2.4			
237	8.1	4.44	7.6	8,800	5.6	24.0	54.0	
238	...	...	...	...	4.0			
239	8.4	5.06	9.5	...	4.6			
240	...	4.42	9.7	7,450	5.1	30.5	69.0	
241	...	4.57	9.8	...	6.9			
242	...	5.70	10.9	...	6.2			
243	8.4	5.68	10.9	...	2.6	34.0	60.0	60 micrograms crystalline Factor I, orally.
244	...	...	...	...	5.4			
245	...	...	...	...	3.0			
246	8.9	5.67	10.0	...	1.6			
247	...	5.74	13.3	...	2.0			
254	9.4	5.85	13.3	4,650	...	40.0	68.4	
261	9.4	6.45	12.6	5,600	...			
289	...	7.55	16.1	7,300	...			

discontinued after 31 days, although the iron and copper were continued. Within 92 days the hemoglobin was again at a low level. Intravenous injections of Factor I was followed by satisfactory hematologic response and gain in weight (Table 1).

Dog 3 when started on diet weighed 6.9 kilos and the red blood cell count was 7.53 million, hemoglobin 16.2 gm., white blood cell count 10,050, hematocrit 56 cc., and mean corpuscular volume 74.3 cubic micra. Iron and ammonium citrate 0.5 gm. and copper sulphate 0.5 mg. were administered daily after the 114th day. This did not prevent an increasing anemia. By the 136th day the red blood cell count was 5.29 million, hemoglobin 7 gm., white cell count 5500, reticulocytes 0.0%, hematocrit 27 cc., mean corpuscular volume 51 cubic micra, and weight 5.5 kilos. Oral administration of crystalline Factor I was initiated (60 micrograms per kilo daily) and was followed 4 days later by a reticulocyte rise of 6.5%. On the 155th day (19th day of treatment) the red blood cell count was 7.61 million, hemoglobin 14.8 gm., white blood cell count 8800, hematocrit 47 cc., mean corpuscular volume 61.8 cubic micra, and weight 6.9 kilos.

**Discussion.** These observations show that adult dogs as well as puppies<sup>3</sup> develop microcytic hypochromic anemia when fed a synthetic diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B<sub>6</sub>). The adult dogs were not allowed to become as anemic as the puppies and this might account for the non-occurrence of convulsions in the adult dogs. Iron and copper did not cure the anemia of 2 dogs to which they were administered. In addition, Dog 2 had recurrence of anemia when the crystalline Factor I was removed from the dietary supplements, although the iron and copper supplements were continued. These observations with the finding of high serum-iron values suggest that this microcytic hypochromic anemia is not the result of lack of absorption of iron from the gastrointestinal tract.

The increase in red blood cells and hemoglobin, improvement in appetite, and increase in weight following oral or intravenous administration of crystalline Factor I was as definite as the previously observed responses following rice bran extracts. These results indicate that the material (Factor I) which cures rat dermatitis is identical with that which cures microcytic hypochromic anemia in dogs.

**Summary.** Adult dogs develop microcytic hypochromic anemia when fed a synthetic casein diet apparently deficient only in Factor I (rat antidermatitis factor, vitamin B<sub>6</sub>). This anemia was cured by addition to the diet, or intravenous injection, of crystalline Factor I.

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## A PERNICIOUS ANEMIA FAMILY.

### FIVE AUTHENTICATED CASES IN THE SAME GENERATION.

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GREAT FALLS, MONTANA.

RICHARD CABOT,<sup>2</sup> in reviewing the 1200 cases of pernicious anemia reported up to 1908, said "that the disease does not appear to be hereditary." Minot<sup>7</sup> in 1920 finds that the occurrence of the disease in members of the same family is not common and that "a hereditary factor is unimportant." In 1927 he<sup>6</sup> says that "while it is true that pernicious anemia may occur in the same family, this is unusual." But 10 years later Castle and Minot<sup>3</sup> state that "when complete histories are available, at least 18% of the patients will be found to have one or more close relatives who have the disease."

In a study of 32 authentic cases treated here in the last 6 years, 6 instances of the occurrence of the disease in some other member of the family have been verified. This is a familial incidence of 18.7% in an insignificant number of cases. It is our impression, however, from the difficulties experienced in obtaining adequate family histories and in verifying cases, that the true familial incidence is probably higher.

Many of the reports<sup>1,4,5,8-10</sup> of instances of 2 or more cases in one family are based on information obtained from the history or received from other members of the family. Many cases are included which have not been studied or do not fulfill the criteria of authenticated cases of the disease. Wilkinson and Brockbank<sup>10</sup> give a summary of many reports whose analyses show few authenticated and numerous presumptive cases. Patek's<sup>9</sup> and Dorst's<sup>4</sup> reports are outstanding; 4 or 5 members of each family, on whom there are adequate data to justify the diagnosis, having died in the pre-liver era.

For this reason one family with 5 proven cases in one generation is reported together with 5 other families in which the existence of another case of the disease has been verified.

All the cases have been studied with a view to fulfilling the following criteria: suggestive clinical symptoms and findings, a blood picture at some time compatible with the disease, an absolute absence of free hydrochloric acid after the administration of histamine, subjective and objective response to potent liver extract and a period of observation sufficiently long to rule out gastrointestinal malignancy.

**Five Authenticated Cases in One Generation.** Four brothers have been under treatment for a long time and the 5th case, a sister, has been under treatment since December, 1938. The 6th member of



the family studied, a sister, does not show any suggestive evidence of the disease. There is one other living member of this family whom it has not been possible to persuade to submit to study.

The 4 brothers were seen somewhere, at some time, in a characteristic relapse and responded typically to liver therapy. In all 5 cases the blood smears showed changes compatible with the blood picture of pernicious anemia. In each case a gastric analysis was obtained which showed no free hydrochloric acid after histamine. The blood Wassermann tests were all negative.

**Case Reports.** CASE 1.—H. L. L. (No. 25356, brother), aged 43 (1939). Onset of symptoms at 35. Diagnosis established May 8, 1934. (This was the first member of this family seen.) Two of his brothers were being treated for pernicious anemia and another one had been ill in 1931, but no definite diagnosis had been made. He recognized the similarity of his symptoms to those of his 2 brothers who were under treatment and he had been taking, without consulting a physician, a mixture of liver and iron for 3 years. Red blood cell count 2.3 million per c.mm., hemoglobin 44% (Sahli). Clinically, he answered Addison's description of a case in relapse. There was no objective evidence of postero-lateral sclerosis. Gastric analysis disclosed a total absence of free hydrochloric acid following histamine. He continues well and active with the red count over 5.0 million per c.mm. on a maintenance dose of 1 cc. of liver concentrate every 21 days.

In the spring of 1935 the diagnosis was confirmed at the Mayo Clinic.

CASE 2. M. B. L. (No. 30172, brother), aged 47 (1939). Onset of symptoms at 38. Diagnosis established April 21, 1930, at the Northwest Clinic, Minot, North Dakota. Red blood cell count, 1.6 million per c.mm., hemoglobin 52%. Gastric analysis showed no free hydrochloric acid after histamine. Seen here first on November 16, 1935. He wished to change from oral to parenteral liver. Red blood cell count was 4.1 million per c.mm. He has remained well and active with the red blood cell count over 5.0 million per c.mm. on 1 cc. liver concentrate every 21 days.

Objectively, at the time I saw him, his general examination was negative including the examination of the central nervous system. In June, 1925, he had been treated for lues at the Mayo Clinic and in January of 1926 the gall bladder was removed there. Both in 1925 and 1926 gastric analyses showed an absence of free hydrochloric acid. Symptoms of the pernicious anemia did not appear until 1930.

CASE 3.—T. J. L. (No. 23604, brother), aged 57 (1939). Onset of symptoms at 49. Diagnosis established December 28, 1935. Red blood cell count 3.8 million per c.mm., hemoglobin 58%. The blood smear showed many well-filled macrocytes. Two subsequent blood counts showed color indices well above one. His color was suggestive; tongue smooth; knee jerks were increased and vibratory sense was diminished to absent in the ankles. His symptoms disappeared promptly with the use of parenteral liver extract. He is well and active with a red blood cell count above 5.0 million per c.mm. on 1 cc. of liver concentrate every 10 days.

He had been seen here in 1931 because of numbness and tingling of the hands and feet. He was seen again in October, 1933, with gastro-intestinal complaints which led to a gastric analysis which showed no free hydrochloric acid after histamine; red blood cell count was 5.0 million per c.mm., hemoglobin 80%. In May, 1934, H. L. L. (Case 1) at my request, urged T. J. L. (Case 3) to report for examination, which he finally did in December, 1935. He was forced to report by increase in severity of symptoms characteristic of pernicious anemia, referred to the gastro-intestinal, cardiovascular and nervous systems.

CASE 4.—J. M. L. (No. 30973, brother), aged 63 (1939). Onset of symptoms at 56. Diagnosis established in 1932, on clinical grounds and on the results of liver therapy, by his local physician. Progressive weakness had made him unable to walk a block. Three and one-half pounds of fresh liver a week brought his hemoglobin from 56 to 87%; no red blood cell count. Gastric analysis at that time showed no free hydrochloric acid; histamine was not given. In only fair health on 4 ounces of powdered liver daily.

He was seen for confirmatory study June 2, 1936. Red blood cell count 3.4 million per c.mm., hemoglobin 80%. Blood smear showed many macrocytes and microcytes. Gastric analysis showed no free hydrochloric acid after histamine. Tongue smooth, color lemonish, knee jerks exaggerated, vibratory sense diminished to absent in both ankles. A change to parenteral liver brought the red count above 5.0 million per c.mm. promptly. He is still well and active with a red blood cell count above 5.0 million per c.mm. on 1 cc. of liver concentrate every 7 days.

CASE 5.—Mrs. L. N. B.,\* sister, aged 66 (1939). Onset of symptoms at 64. Diagnosis established August, 1938. The following data obtained by correspondence: On July 22, 1938, the red blood cell count was 3.4 million per c.mm., hemoglobin 81%, and a gastric analysis showed an absence of free hydrochloric acid; no histamine. On August, 18, 1938, the gastric analysis was repeated and showed no free hydrochloric acid after histamine. The red blood count, repeated on this date had dropped to 3.0 million per c.mm., hemoglobin 80%. Blood smears forwarded from the local laboratory showed many well-filled macrocytes and a few microcytes. She had been receiving medical attention since 1937 for paresthesias of the hands and feet. By December, 1938, her general condition was much worse; she was placed on parenteral liver therapy and is now (June, 1939) much improved.

NOTE: Mrs. J. C. C. (No. 38035, sister), aged 55 (1939). Reported for study on March 31, 1938. Nothing suggestive of pernicious anemia subjectively or objectively. Red blood cell count was 4.7 million per c.mm., hemoglobin 86%. The blood smear was normal in appearance. Gastric analysis showed an abundance of free hydrochloric acid without histamine.

NOTE.—E. R. L., brother, living in Nevada, aged 50. Neither the author nor the other members of the family, who have been most coöperative during the 5 years of this study, have been successful in persuading him to submit to examination.

#### TWO CASES IN EACH OF FIVE FAMILIES.

CASE 6.—A. O. T. (No. 18394, seen here), aged 32 (1939). Onset of symptoms at 24. Diagnosis established January, 1931. Red blood cell count 1.7 million per c.mm., hemoglobin, 50%. Repeated gastric analyses have failed to show free hydrochloric acid after histamine. Relapse in June, 1932, red blood cell count 1.5 million per c.mm., hemoglobin, 37%. Relapse in 1935, red blood cell count 1.4 million per c.mm., hemoglobin, 32%. In 1935 he showed marked objective evidence of combined sclerosis. He responded well to liver therapy at the time of each relapse. Since 1935 arrangements have been made so that he obtains parenteral liver regularly. He works, slightly handicapped by his cord changes.

CASE 7.—Mrs. C. T. T. (No. 5669, seen here, mother of A. O. T.), aged 67 (1939). Onset of symptoms at 63. Diagnosis established September 9, 1936. Red blood cell count 1.9 million per c.mm., hemoglobin, 30%. Gastric analysis showed no free hydrochloric after histamine. Vibratory sense in the ankles was absent. Roentgen-rays of the stomach and colon showed no evidence of malignancy. She made a typical therapeutic response to liver extract. In only fair health since, she is irregular about her liver and the red blood cell count is rarely well up.

\* Information through the courtesy of Dr. A. J. Lewis, Henning, Minn., and Mildred Nichols, R.N., Wadena, Minn.

Three years before the establishment of the diagnosis she was seen with the complaint of fatigability; red blood cell count then was 3.3 million per c.mm.; hemoglobin, 58%. Diagnosis confirmed in 1937 by Dr. L. J. Meienberg, Portland, Oregon.

CASE 8.—Mrs. D. A. S. (No. 13568, seen here), aged 48 (1939). Onset of symptoms at 39. Diagnosis established in January, 1930. Gastric analysis showed no free hydrochloric acid after histamine. Subjective symptoms of numbness of the hands and feet. Blood smears showed a picture compatible with pernicious anemia. Carried on oral liver until relapse in 1936; moderate spinal cord changes. Lowest red blood cell count 3.0 million per c.mm.; hemoglobin, 60%. Therapy complicated by the presence of myxedema. Typical therapeutic response to larger than usual doses of liver. Maintained in good health at about 5.0 million red blood cells per c.mm. on 5 cc. of liver extract each week up to the present time.

CASE 9.—L. H. B.\* (No. 16509, brother of Mrs. D. A. S), aged 65 (1939). Minimum red blood cell count report showed 2.6 million per c.mm. After the first use of liver extract a count was obtained on October 27, 1938, which showed 3.4 million per c.mm.; hemoglobin, 80%. Blood smear was perfectly compatible with pernicious anemia. The gastric analysis showed no free hydrochloric acid after histamine.

CASE 10.—R. M. (No. 38075, seen here), aged 71 (1939). Onset of symptoms at 69. Diagnosis established in March, 1938. Red blood cell count 4.6 million per c.mm.; hemoglobin, 88%. The blood smear showed many macrocytes and microcytes and in other features was entirely compatible with pernicious anemia. In spite of the high red blood cell count, there was evidence of advanced spinal cord involvement; total absence of vibratory sense in both ankles and a strikingly abnormal gait. The gastric analysis showed no free hydrochloric acid after histamine. He refused treatment for a month during which time he became unable to walk. Responded slowly but steadily to large doses of parenteral liver daily for many weeks. At present, he is in good health except for some residual disturbances and gets about actively without the use of a cane. His maintenance dose is 3 cc. of liver concentrate derived from 100 gm. of liver, every 5 days.

CASE 11.—J. J. M.,† (brother of R. M.), seen in February, 1925, in the Jefferson Medical School Hospital on account of a sore mouth and paresthesias of the extremities. Red blood cell count 2.2 million per c.mm.; hemoglobin, 52%. Roentgen-rays of the stomach led to an exploratory operation which disclosed no malignancy. Red blood cell count 2.2 million per c.mm.; hemoglobin, 57% in July, 1925. Total absence of free hydrochloric acid in the gastric analysis (histamine was not used). He was not seen after July, 1925. He became helpless and died of "anemia and paralysis" about a year later. No liver therapy.

CASE 12.—Mrs. L. M. C. (No. 36653, seen here), died January, 1938, at the age of 71, of cardiovascular disease. Onset of symptoms at 66. Diagnosis established in 1932 at the Mayo Clinic. Records available show fairly satisfactory maintenance through 1935, following which she had no medical attention until she was admitted to the hospital on September 28, 1937, with a red blood cell count of 1.4 million per c.mm.; hemoglobin, 46%. Prompt response to heavy dosage of parenteral liver brought the blood to 4.0 million per c.mm.; hemoglobin to 84%. Maximum reticulocyte response 40%. Vibratory sensation was absent in the ankles.

CASE 13.—H. G. B.‡ (brother of Mrs. L. M. C.), aged 62 (1939). Onset of symptoms at 57. Diagnosis established at the County Hospital, Los Angeles, at time of relapse. Blood data not available. He made the

\* Verification through the courtesy of Dr. H. W. Pfeiffer, La Mesa, California.

† Verification through the courtesy of Dr. E. J. G. Beardsley, Philadelphia.

‡ Verification through the courtesy of Dr. J. M. Askey, Los Angeles.

typical response to oral liver, on large doses of which he has done well for 5 years. Examination on April 10, 1939, showed an absence of vibratory sense in both ankles with increased patellar jerks.

CASE 14.—Mrs. C. A. B. (No. 04431, seen here), aged 66 (1939). Onset of symptoms in 1928. Diagnosis established August, 1928. Red blood cell count, 2.1 million per c.mm.; hemoglobin, 70%. Liver and powdered liver extract orally gave unsatisfactory maintenance and disabling spinal cord changes by 1932. Histamine achlorhydria. Improved since, with red blood cell count maintained above 4.5 million per c.mm. on 3 cc. liver concentrate every 7 days.

CASE 15.—J. S.\* (brother of Mrs. C. A. B.), aged 63 (1939). Onset of symptoms in 1926. Diagnosis established in June, 1927, at the University Hospital, Ann Arbor, Mich. Red blood cell count, 2.4 million per c.mm.; hemoglobin, 49%. Typical response to whole liver. Histamine achlorhydria. Well and active since on diet of whole liver. Red blood cell count in April, 1938, 4.9 million per c.mm.; hemoglobin, 96%, at the Simpson Memorial Institute.

**Comment.**—Meulengracht<sup>8</sup> pointed out the difficulties inherent in any study of the familial incidence of this disease; difficulties due to errors in diagnoses, to the scattering of families, and to the development of the disease late in life. Five years were required to obtain the data on the few cases reported here and the data had to be obtained from widely separated geographical points (Philadelphia to Los Angeles). The mother of the son who developed the disease at age 24 did not herself develop the disease until age 63; her death at age 60 of pneumonia would have excluded these cases from the study. The physician in practice can best follow several generations of a family and he is, therefore, in an enviable position for the accumulation of data.

The practical value of an appreciation of the true familial incidence of the disease is as great as in diabetes mellitus. It justifies anticipatory studies which should lead to the earlier recognition of the disease, especially in those cases in which "diagnostic" blood changes lag well behind spinal cord changes.

**Summary.** 1. A pernicious anemia family is reported with 5 authenticated cases in one generation.

2. Two cases are reported in each of 5 other families.

3. In this small series of cases the percentage of familial incidence is 18.7% which approaches the 18% found by Castle and Minot.

4. It is suggested that the true incidence is higher and that an appreciation of the familial incidence has definite practical value.

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\* Verification through the courtesy of Dr. R. Isaacs, Ann Arbor, Mich.

## SOME OBSERVATIONS UPON A CASE OF HEREDITARY HEMOLYTIC JAUNDICE.

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IN 1935 the senior author<sup>3</sup> reported studies on a case of pernicious anemia in an individual having hereditary hemolytic jaundice. It was pointed out that in spite of the presence of the pernicious anemia the erythrocytes maintained the relatively small diameter and spherical shape of hemolytic jaundice. Following liver therapy, marked improvement occurred and all evidence of pernicious anemia disappeared. However, the characteristic features of hemolytic jaundice have persisted and are uninfluenced by the therapy. On two occasions since his discharge from the hospital the patient has neglected to take his liver extract and a recurrence of the pernicious anemia has taken place, but in each case improvement followed a return to adequate treatment. Because of the age of this patient (67) it has not been considered advisable to recommend splenectomy.

At the time this study was reported, blood studies were carried out on 3 of his children and hemolytic jaundice was found to be present in 1 son, then 32 years of age. This individual showed no evidence of pernicious anemia and gastric analysis revealed free hydrochloric acid. The spleen was large, extending 10.5 cm. below the border of the ribs, and he was advised to have it removed. He would not consent, however, and his health was not markedly disturbed by the condition. In the interval he has remained quite well, but recently a severe exacerbation brought him to the hospital and consent was obtained to proceed with the splenectomy. As opportunity was thus given to make detailed studies on a case of hereditary hemolytic jaundice which had been under observation for some time, special examinations were carried out. Because of the more precise methods in estimating hemolysis of the erythrocytes and bilirubinemia made possible by the use of the Evelyn photoelectric colorimeter, certain new facts were brought out by these studies and it is the purpose of this communication to present them to the literature.

**Clinical History.** The patient was admitted to this hospital on Jan. 3, 1939, with complaints of: 1, increasing jaundice of 4 days' duration; 2, pain in the left side of the abdomen and left shoulder continuously for 4 days; and 3, vomiting on 1 occasion 4 days prior to admission. The patient complained that the pain in his left side and left shoulder was worse

upon lying down flat. He had noticed that his jaundice appeared to be deeper at intervals ranging from 10 days to a month over a period of many years, also that any slight infection, especially of the upper respiratory tract, made it more pronounced. He had never had an attack associated with pain in the left shoulder and left side of the abdomen previous to the one from which he was suffering.

*Physical examination* revealed temp. 100.6° F., pulse 112, respirations 22 per minute. Blood pressure 132/75. There was a moderate degree of jaundice. The abdomen was slightly distended. The liver was palpable 2 finger-breadths below the costal margin. The spleen was 3 finger-breadths below the costal margin and was exquisitely tender. Physical examination was otherwise negative. Roentgen rays of the chest and abdomen revealed gross enlargement of the spleen, slight elevation of the left diaphragm with left diaphragmatic pleuritis. A diagnosis of familial hemolytic jaundice, left diaphragmatic pleuritis and upper respiratory infection was made.

*Clinical Notes and Progress.* On admission to the hospital on January 3 the patient was in the midst of a severe attack of jaundice. This gradually subsided, with clinical improvement of the patient, until Feb. 3, 1939, at which time he suffered a recurrence of the upper respiratory infection and an accompanying increase in jaundice. There was gradual clinical improvement with subsidence of the upper respiratory infection and decrease in symptoms until the time of operation.

The patient's spleen was removed on February 10. Following operation there was a marked increase in upper respiratory symptoms but a definitely progressive improvement in jaundice and relief of pains. He was discharged on March 6, at which time jaundice had completely disappeared and there was no evidence of infection. Follow-up examination on April 21, 1939, showed the patient to be free of jaundice and to have gained 20 pounds in weight since discharge from the hospital.

*Pathologic Examination.* The spleen was large (1750 gm.) and markedly hemorrhagic in appearance. There was a large subcapsular hematoma at the upper pole. The capsule was densely thickened by fibrous tissue. Microscopic examination showed the pulp to be stuffed with blood while the venous sinuses were collapsed. The spleen was therefore typical of that found in hereditary hemolytic jaundice.

*Hematologic Examination* (first, Feb., 1937). *Bilirubinemia.* At that time he appeared to be suffering from one of the exacerbations of jaundice to which he was subject. The blood bilirubin at that time showed a total bilirubin of 28 units van den Bergh. The prompt direct van den Bergh reaction was negative; the delayed direct reaction was strongly positive. Photoelectric determinations were unfortunately not available at that time.

On admission to the hospital, January 3, 1939, the patient was again in the midst of a severe attack of jaundice. At that time the total bilirubinemia, as determined by the method of Malloy and Evelyn,<sup>2</sup> was 11 mg. per 100 cc., of which 2.31 mg. gave the direct reaction. The direct reaction was 51% complete at the end of  $\frac{1}{2}$  minute and 100% complete at the end of 10 minutes.

Following hospitalization the patient showed considerable improvement, with decreasing bilirubinemia (see Chart 1), so that 18 days after entering hospital the total bilirubinemia had reached 3.9 mg. per 100 cc., of which 0.73 mg. was present in the direct reaction. This was 51% complete at the end of  $\frac{1}{2}$  minute and 85% complete at the end of 10 minutes.

On February 3, the patient suffered an exacerbation of his jaundice, accompanied by an increase in the size of the spleen and corresponding increase in the pains in the left side of his abdomen and left shoulder. On the thirtieth day after admission the total bilirubinemia was 6.5 mg., of

which 0.81 mg. gave the direct reaction. This was 51% complete at the end of  $\frac{1}{2}$  minute and 84% complete at the end of 10 minutes.

Following this episode there was a period of clinical improvement and on the day preceding operation the patient showed a total blood bilirubin of 4.8 mg. per 100 cc., of which 0.68 mg. was direct bilirubin. The direct reaction was 17% complete at the end of  $\frac{1}{2}$  minute and 93% complete at the end of 10 minutes.

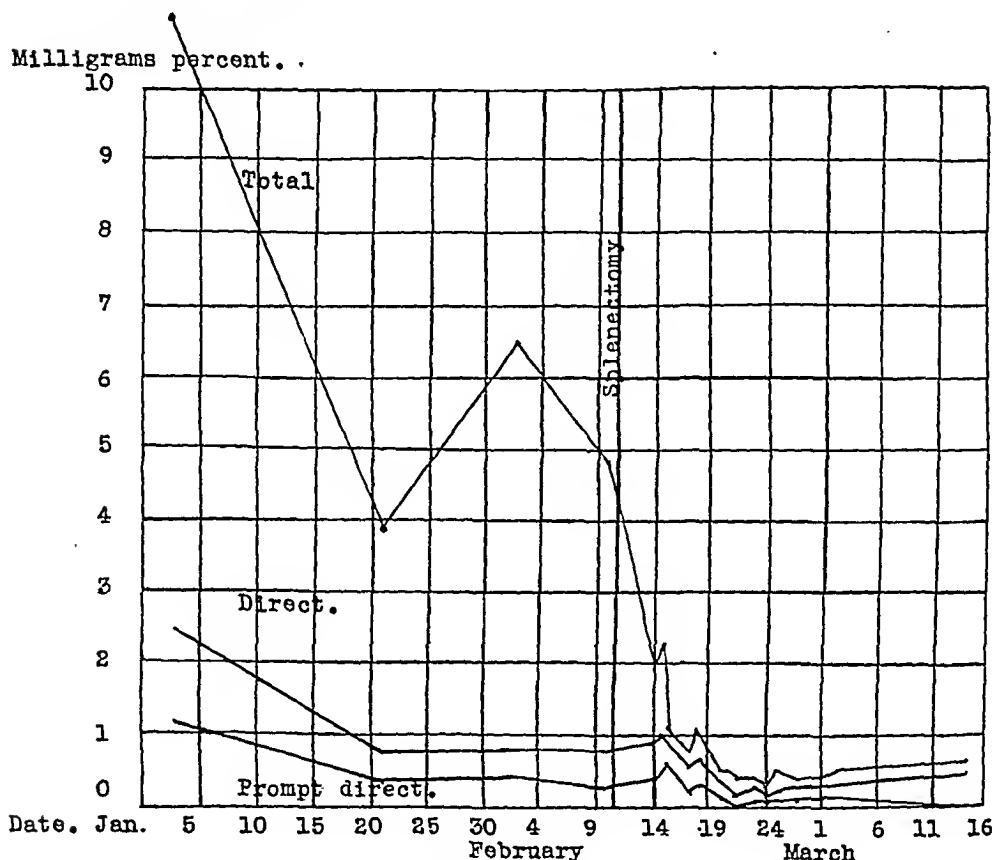


CHART 1.—Hereditary hemolytic jaundice. Bilirubinemia.

Splenectomy was performed on February 11. Two days later the bilirubinemia had dropped to 2.6 mg. per 100 cc., of which 0.91 mg. was direct bilirubin. The direct reaction was 31% complete at the end of  $\frac{1}{2}$  minute and 88% complete within 10 minutes.

Following this the bilirubin dropped rapidly so that 6 days after operation the total bilirubin was below 1 mg.; 9 days after the total bilirubinemia was close to normal limits. Jaundice disappeared clinically at the same time and has not recurred. Thirty-four days after operation the total bilirubin of the blood was 0.68 mg., of which 0.33 mg. was contained in the direct reaction. The immediate direct reaction was negative at  $\frac{1}{2}$  minute and 33% complete at the end of 10 minutes.

As has been recognized for some time, our findings show that this hyperbilirubinemia of hemolytic jaundice is due principally to the large amount of bilirubin in the circulating blood giving the indirect

reaction. The finer details of the photoelectric method reveal, however, that there is an appreciable increase in the direct-reacting bilirubin which rises somewhat in exacerbations but tends to maintain a fairly constant level of approximately 0.7 to 0.9 mg. per 100 cc. Following splenectomy there occurs a precipitous fall in indirect bilirubin with an accompanying slight rise in the direct bilirubin. Finally, after the total bilirubin has reached a figure of about 1 mg. the two types gradually fall together to essentially normal levels.

*Red Blood Cell Fragility.* Studies in the fragility of the erythrocytes to hypotonic solutions of salt were carried out, using the recently published method of Waugh and Asherman.<sup>4</sup> By this method the resistance of the cells may be expressed either as an

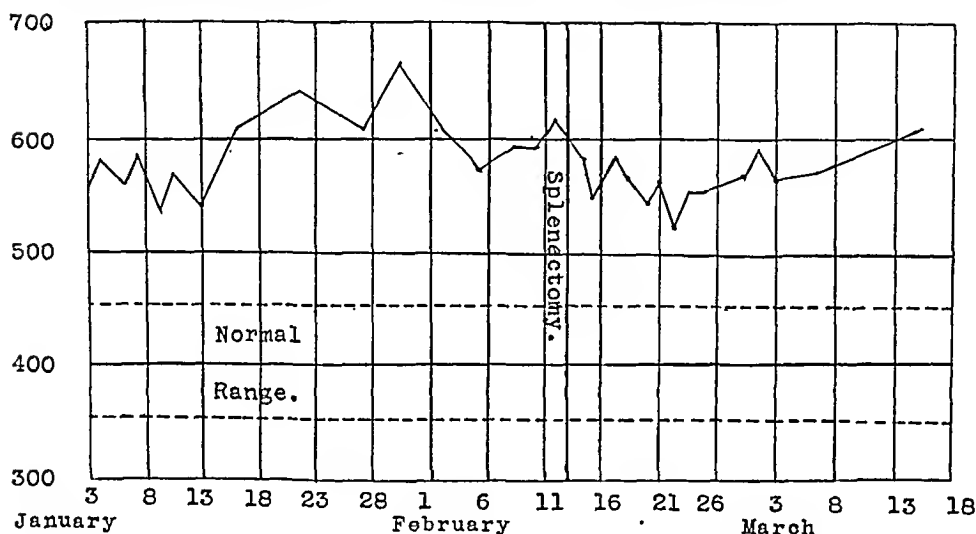


CHART 2.—Hereditary hemolytic jaundice. Index of hemolysis (before and after splenectomy).

index, which has a normal range from 350 to 450 and which falls as low as 250 in cases with lessened, and as high as 750 in increased fragility, or as a so-called hemolygram in which a chart expressing the character of the curve of resistance throughout the different concentrations is employed.

The index of hemolysis in this case was found to be consistently well above normal limits (Chart 2) and at a relatively constant level, which tended to fall slightly following operation but subsequently rose to its previous figure. It is well known that splenectomy produces an increase in the resistance even in normal individuals (accident cases), so this fall is rather to be expected. It is noteworthy, however, that the increased fragility persists even though the excessive destruction of the erythrocytes ceases when the spleen is removed.

By the use of the hemolygram (Chart 3), an interesting change in the character of the fragility curves before, as compared with those



after operation, was disclosed. It will be noted that during the preoperative period the curve becomes distinctly irregular in the higher concentrations, due to the presence of a number of cells which hemolyzed in the higher, even isotonic solutions. This feature, which was persistent before, however, completely disappeared after operation and the curve then became quite regular and similar to the normal, though displaying a distinct shift of position toward an increased fragility.

Percentage  
Hemolysis.

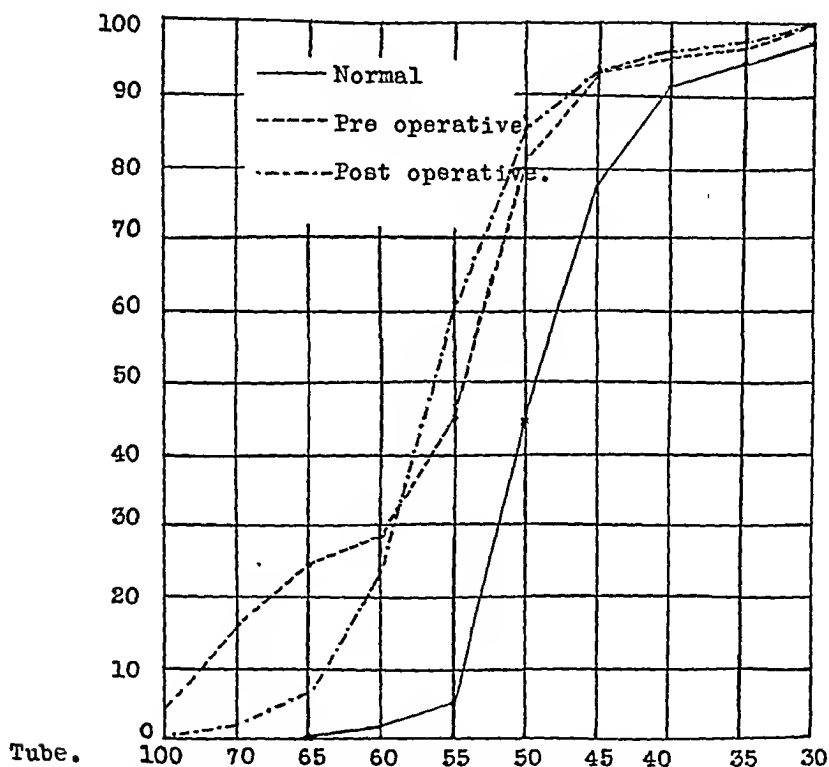


CHART 3.—Hereditary hemolytic jaundice. Hemolygram.

Removal of the spleen evidently caused the disappearance from the blood of a certain percentage of extremely fragile cells, while the great majority of the erythrocytes remained as before. As the reticulocytes tend to decrease after operation, one might surmise that they are the forms concerned. Such an opinion does not agree with the generally accepted view that reticulocytes are not unusually fragile. While we are unable to explain this peculiar change, we cannot help but feel that it may be of considerable significance and, if it is found to be present in other cases of this disease, may even be considered as a possible explanation of the beneficial effect of splenectomy.

*Red Blood Cell Diameter.* Studies of the diameter of the erythrocytes were made by a specially constructed apparatus whereby the cells are projected at a magnification of 5000 onto a ground glass

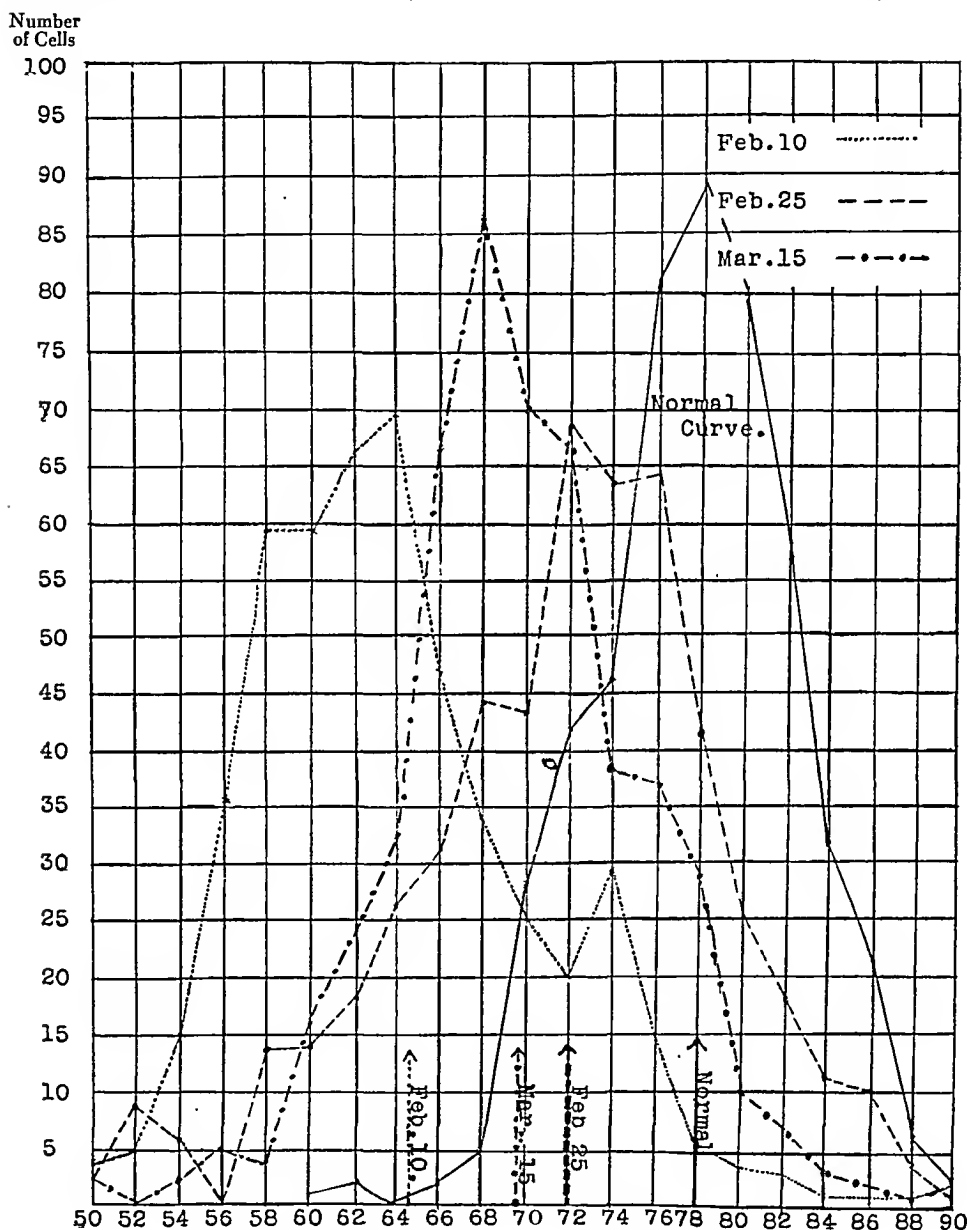


CHART 4.—Hereditary hemolytic jaundice. Price-Jones curves. Mean corpuscle diameters of individual cells in 0.1 microns. Arrows indicate computed average corpuscle diameters.

plate. The maximum and minimum diameter of 500 cells are recorded and from this a so-called Price-Jones curve is constructed and the average diameter computed. In Chart 4, several of these

curves are shown together with a normal for comparison. It will be noted that on February 10, just prior to splenectomy, the average diameter of the erythrocytes was 6.44 microns, in contrast to the normal of 7.8 microns. The lowness of the peak and the great spread of the base of the curve show graphically the marked anisocytosis which was present. Following splenectomy, the average diameter first rose to 7.2 microns with, however, still marked variation in the size of the elements. This was during the period of temporary lowering of the fragility and quite probably indicated an appearance of flattening, less spherical but not necessarily larger erythrocytes. There then occurred, with improvement in the anemia, a shift to cells of smaller but more uniform diameter and with this an increase in the fragility. At the time of the patient's discharge from the hospital, the peak of this curve had reached essentially the same height met with normally.

*Red Blood Cell Enumerations.* Previous to splenectomy the red blood cell count had never exceeded 3,800,000 on any occasion. Following splenectomy the red blood cell count increased gradually until on the thirty-second day after operation it reached 4,700,000 per c.mm. of blood.

*Hemoglobin Determinations.* Hemoglobin was measured by the photoelectric colorimeter with 15.6 gm. per 100 cc. taken as equivalent to 100%. Before operation the figures varied between 54 and 68%. The lower readings were encountered as would be expected during exacerbations when the bilirubinemia was high. Following splenectomy there occurred a quite steady rise to 96% at our last examination (Chart 5). At all times the hemoglobin concentration, *i. e.*, the relation of hemoglobin to corpuscle material, was at a high figure.

*Corpuscle Volume and Average Corpuscle Volume.* Previous to operation the corpuscle volume had never exceeded 34% of the total blood volume. Following operation there was a gradual and steady increase in corpuscle volume, paralleling the increase in hemoglobin and red cells, up to 45% of the total blood volume (Chart 5).

The average corpuscle volume previous to operation, determined from a moderately large number of observations, was 90 cubic microns. This figure is slightly lower than normal (95 cubic microns) but relatively high considering the small diameter of the cells. This peculiarity of the erythrocytes in hemolytic jaundice is well recognized and has led to the use of the term spherocytes, indicating a cell of spherical, rather than biconcave shape. This alteration of shape is now generally accepted as the explanation for the increased fragility. After splenectomy the average corpuscle volume fell somewhat but the general spherical character of the cells was preserved.

*Reticulocyte Counts.* Reticulocyte counts done before operation showed levels often as high as 15%, and never below 1% of the

total red blood cells. Following operation, the reticulocytes in the circulation rapidly decreased so that within 12 days they had reached normal levels or less than 1%. Thus, as has often been shown before, with the cessation of abnormal blood destruction after splenectomy, hurried regeneration and the discharge of many immature erythrocytes into the blood stream no longer occur.

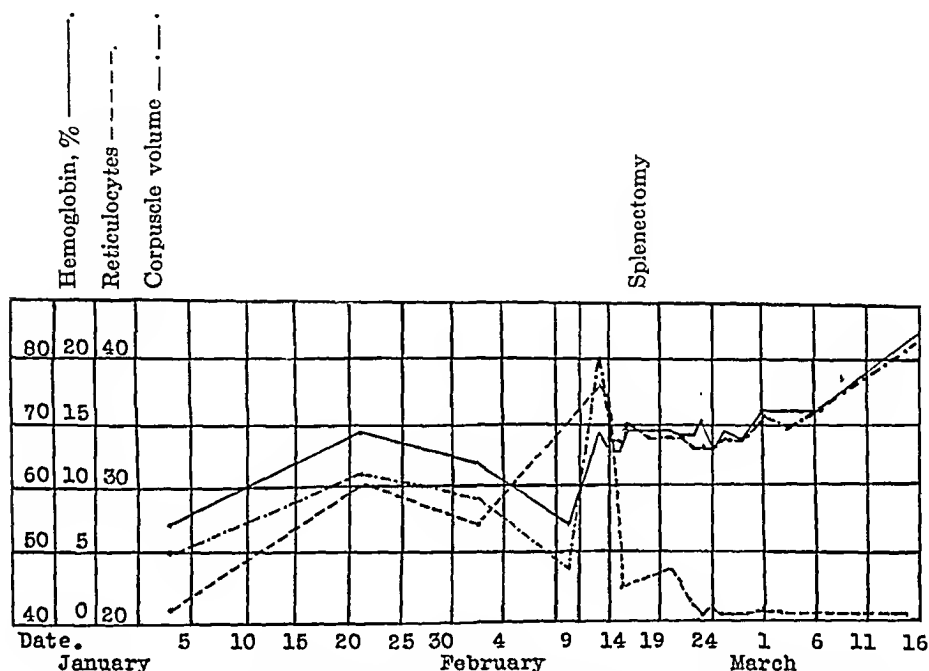


CHART 5.—Hereditary hemolytic jaundice. Hemoglobin, corpuscle volume and reticulocyte count.

*Platelet Counts.* Enumeration of the thrombocytes carried out during the period preceding operation showed the platelets to vary between 135,000 and 330,000 per c.mm. of blood. On the fourth day following splenectomy the count reached 610,000 per c.mm., a definite elevation above normal. This elevation persisted for 1 month, at the end of which time it gradually fell to normal.

*Leukocyte Counts and Differential Leukocyte Counts.* Prior to operation the blood showed a constant leukocytosis of around 9000. This was due to an increase in the myeloid elements. Following splenectomy there was a sharp rise to 40,000 due to the pouring into the blood of neutrophils, eosinophils and monocytes. This gradually fell off until by March 1 it again reached 9000, which level has been maintained. Such a moderate persistent increase in the white blood cells is usual following removal of the spleen.

*Study of the Blood Serum to Determine the Presence or Absence of Hemolysins.* Previous to operation an attempt was made to determine the presence of hemolysins in the blood serum of the patient, as

suggested by Dameshek and Schwartz<sup>1</sup> in their article on acquired hemolytic jaundice.

The technique of the investigation was as follows: The patient's blood was allowed to clot for at least 4 hours and the serum withdrawn. Increasing dilutions from 1 to 2 to 1 to 2048 were made up in 11 tubes. A suspension of red blood cells from the patient and other sources, as mentioned below, was prepared by washing the red cells three times in saline and making up a saline suspension containing 1% red blood cells. Titrations were carried out with the above dilutions of serum in 0.5 cc. amounts, to which were added 0.5 cc. of the red blood cells suspension.

Repeat titrations were carried out using serum which had been heated to 56° C. for 30 minutes. To this was added an excess of a solution of complement of known potency. Readings of all titrations were made after incubating the titration for 2 hours at 37°; secondly, after 18 hours in the refrigerator and, thirdly, after re-incubating the tubes at 37° for 2 hours.

The patient's cells were determined to be Type O (Landsteiner), and therefore contained no agglutinogens; whereas the patient's serum was assumed to contain agglutinins A and B. For this reason the patient's serum could be tested against other Type O cells for hemolytic action upon them. This was carried out as above described. Control experiments were done, using Type O cells and serum containing agglutinins A and B from other individuals than the patient.

EXPERIMENT 1. Here the patient's own serum was tested against the patient's washed cells. No hemolysis occurred in any dilution in any of the three readings.

EXPERIMENT 2. The patient's serum, heated to 56° for 30 minutes was tested against the patient's washed cells, excess complement in the form of diluted guinea pig serum being added. No hemolysis occurred in any tube in any of the three readings.

EXPERIMENT 3. The patient's serum was tested against Type O cells which previously had shown no signs of agglutination with the patient's serum, to obviate any error that might arise from using cells which might contain agglutinogens not tested for with the routine serum. There was no evidence of any hemolysis in any of the three readings in any of the tubes.

EXPERIMENT 4. The patient's serum, heated to 56° C. for 30 minutes was tested against Type O cells which fulfilled the characteristics sought in Experiment 3. Excess complement was added to each tube. No hemolysis occurred in any of the tubes on any of the three readings.

EXPERIMENT 5. Type O cells were tested against the serum from the same individual, not the patient. No hemolysis occurred in any tube.

Our experiments, therefore, failed to demonstrate the presence

of any hemolysin which could be brought into causal relation with the excessive destruction of the erythrocytes which was present.

**Summary.** Special detailed hematologic studies carried out in a case of hereditary hemolytic jaundice before and after splenectomy, besides substantiating many well-known facts, reveal:

1. The direct-reacting bilirubin of the blood plasma tends, in contrast to the indirect-reacting portion, to maintain a relatively constant level, even during exacerbations; rises slightly immediately following splenectomy and then falls when the total bilirubin reaches 1 mg. per 100 cc. to normal levels.

2. The hemolytic index of the erythrocytes is not appreciably altered by splenectomy except for a temporary slight fall immediately following operation.

3. There are present in the circulating blood before operation a small percentage of extremely fragile cells, and these disappear after splenectomy, though the vast majority of the cells are apparently not altered in their behavior to hypotonic salt solution.

4. No hemolysins for the patient's own cells or cells of a like group are present in the plasma.

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## THE POTENCY OF BLOOD-COAGULATING SUBSTANCES.

### A BIOLOGIC ASSAY.\*

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THERE are, in general, three types of hemostatic agents: those that act by decreasing the blood flow, those that promote repair of diseased blood-vessels, and those that increase the coagulability of the blood. In effective dosage, many of the substances of the third group cause toxic reactions, induce necrosis, or produce widespread intravascular coagulation.

When contemplating the use of a blood-coagulating substance, it is important to know the answers to three questions: Is the

\* Assisted by a grant from the Christine Breon Fund.

substance safe to administer? How effective is it *in vivo*? What is its potency *in vitro*? This paper deals with the biologic assay of the potency of a group of commercially available substances purporting to increase the coagulability of the blood.

It can be shown experimentally *in vitro* that the coagulation of the blood does not take place according to the law of mass action. The coagulation of the blood cannot be accelerated by the indiscriminate addition of an excess of any of the basic substances involved in the reaction. Only those substances that increase the concentration of thrombin or supply a thrombin-like element serve to increase the speed of blood coagulation.

According to Morawitz, the present generally accepted hypothesis of the mechanism of blood coagulation is based on the following reactions:

1. Prothrombin + thromboplastin + calcium  $\rightarrow$  thrombin

2. Thrombin + fibrinogen  $\rightarrow$  fibrin

*Thromboplastin.* The addition of thromboplastin to blood will shorten the clotting time. Until a certain limit is reached, the decrease in coagulation time is proportional to the concentration of thromboplastin. This is due to the more rapid conversion of prothrombin to thrombin. When all of the prothrombin has been converted to thrombin, the addition of further thromboplastin will not shorten the coagulation time.

*Calcium.* According to Crane and Sanford,<sup>3</sup> the concentration of calcium in whole blood may be varied between wide limits without altering the coagulation time. Aggeler and Lucia<sup>1,9</sup> have demonstrated an optimum concentration for the recalcification of oxalated plasma. The salutary effect of calcium in obstructive jaundice is not due to any direct effect of calcium on the blood-coagulation mechanism but may be due to improvement in the function of the liver.

*Prothrombin.* Quick<sup>12</sup> showed that the coagulation time of prothrombin-deficient plasma (when thromboplastin is present in excess) is prolonged in proportion to the degree of prothrombin deficiency. The addition of prothrombin to prothrombin-deficient plasma will restore the prolonged coagulation time to normal.

*Fibrinogen.* Mills<sup>10</sup> advanced the following hypothesis of the mechanism of blood coagulation in wounds: Blood fibrinogen + calcium + tissue fibrinogen  $\rightarrow$  fibrin. This work has, however, not been substantiated.<sup>6</sup> Smith and his co-workers,<sup>13</sup> Davison<sup>4</sup> and Quick<sup>11</sup> working with solutions of *purified* tissue fibrinogen could not verify Mills' conclusions. According to the literature, the source and concentration of fibrinogen have little influence on the clotting time. In its effect on blood coagulation, there is no essential difference between blood fibrinogen and tissue fibrinogen. The addition of purified fibrinogen to normal plasma does not increase the speed of coagulation.

The addition to blood of different varieties of snake venom will shorten the coagulation time. Eagle<sup>5</sup> has shown that the coagulative action of these venoms is probably due to their content of proteolytic enzymes. Some of these enzymes convert prothrombin to thrombin, and some convert fibrinogen to fibrin. Some types of venoms contain both enzymes.

**Material Studied.** The coagulative potency of 17 commercially available products for hastening the process of blood coagulation was tested. These included two varieties of snake venom, five thromboplastin solutions for local or oral administration, five thromboplastin solutions for hypodermic use, one tissue fibrinogen solution for oral use, one tissue fibrinogen solution for hypodermic use, one substance derived from bovine blood for oral, local or hypodermic use, and two types of refined horse serum for hypodermic use.

The two venoms studied were the Fer-de-lance (*Bothrops atrox*) and Russell viper (*Daboia russellii*). The Fer-de-lance venom is dispensed as a 1 to 5000 solution. The Russell viper venom is dispensed as a powder, 0.1 mg., to which is added 1 cc. of solvent, resulting in a 1 to 10,000 solution.

The five thromboplastin solutions were derived from bovine brain. Those intended for local or oral use are made by the method of Hess,<sup>8</sup> slightly modified. They consist of tissue fluids containing finely ground particles suspended in physiologic saline. The thromboplastin solutions for hypodermic administration are made by dilution, after removal of coagulated proteins and particulate matter, of the material used in the preparation of the local or oral product.

Both the tissue fibrinogen preparation for oral use, and that for hypodermic administration are stated to contain 0.5% cephalin and 1.5% tissue fibrinogen, and are derived from beef lung.

The bovine blood derivative is made by a complicated process of extraction with lipid solvents. It is stated to contain "certain natural coagulating elements necessary for clotting the blood."

The coagulative action of the two types of horse serum is stated to depend upon the content of thromboplastin. Both have been concentrated and refined so as to reduce their protein content. "The protein has been totally removed" from Product 16, and the potency of Product 17 has been "enhanced by the addition of bovine testicular extract."

For comparative purposes and tests, solutions of thromboplastin similar to those recommended for local, oral and hypodermic use were made from fresh sheep, rabbit, dog, horse and guinea-pig brain.

**Method.** The choice of a test plasma is of paramount importance. Quick<sup>11</sup> has shown that thromboplastin is, to some extent, specific for the species. Tissue extract of one species, when added to the blood of another species, may show only slight thromboplastic potency; conversely, the blood of one species may respond to a lesser degree to tissue extracts of other species. Preparations of thromboplastin are less active in human plasma than in the plasma of common laboratory animals. Since these agents



are intended for use in human subjects, the only valid test of their potency must be the degree of their activity in human blood. It is of no practical significance that a product will shorten the coagulation time of rabbit blood from 15 minutes to 15 seconds if it has little or no potency in human blood. In all of these experiments, human plasma has been used, and this fact may account partly for the great discrepancy between our findings and the claims made by the manufacturers of these products.

All tests were completed within 1 hour after the blood was withdrawn. It is essential that this time limit be observed, since there is a variable and marked prolongation of the coagulation time when plasma has been allowed to stand longer. The test materials were kept at 0° C. until used. The precautions of Hanzlik and Weidenthal<sup>7</sup> were observed. Testing materials were discarded within 8 hours after the packages were opened. All test materials used were well within their stated expiration dates. Contrary to the observations of Quick<sup>11</sup> and Hanzlik and Weidenthal,<sup>7</sup> Aggeler and Lucia<sup>1</sup> have demonstrated that an optimum concentration of thromboplastin solution is required in order to induce a maximum shortening of the coagulation time of the plasma. For this reason we studied all the products throughout a wide range of dilution. Specimens of both normal and hemophilic plasma were used. Three samples of each product were tested. Five series of tests of each product were performed with specimens of normal plasma, and two series of tests of each product were performed with specimens of hemophilic plasma. The final results are expressed as the average of each series of tests.

The full strength of each product as dispensed by the manufacturer was diluted by serial half-dilutions down to 1/1024 of the original strength. The dilutions were made with 0.85% NaCl. One-tenth cubic centimeter of each dilution was pipetted into clean 13 by 100 mm. glass tubes. One-tenth cubic centimeter of 0.275%  $\text{CaCl}_2$  was added to each, and the tubes were placed in a water bath at 37° C. Nine cubic centimeters of blood were withdrawn from the antecubital vein, mixed quickly with 1 cc. of 1.34% sodium oxalate in a test tube and centrifugalized at 2000 r.p.m. for 10 minutes. The supernatant plasma was transferred to a test tube which was placed in the water bath and allowed to stand for 10 minutes before being used in the tests.

One-tenth cubic centimeter of plasma was pipetted into the mixture of hemostatic agent and  $\text{CaCl}_2$ . The tube was agitated thoroughly for 5 seconds and the time of coagulation was noted with a stop watch. The test was performed with each dilution of hemostatic agent in turn. Control tests were performed using only 1/10 cc. 0.85% NaCl in place of the hemostatic agent. In order to obtain a satisfactory degree of accuracy, duplicate readings were made varying in time not more than a few seconds from the originals. Most of the agents studied were employed in such concentrations as to yield, upon dilution, a range of concentrations with optimum activity. The actual concentration showing maximum activity is of much less significance than the degree of activity of a substance when present in the optimum concentration, and the range of dilutions through which that activity is distinctly manifested.

Similar series of tests were performed\* using hemophilic and heparinized normal whole blood. The coagulation times of the specimens of hemophilic blood ranged from 45 to 55 minutes. The coagulation times of the specimens of normal blood were prolonged to between 45 and 55 minutes by the addition of 1 unit of heparin\* to each 2 cc. of blood. To perform the test, 0.1 cc. of a dilution of each hemostatic agent was mixed with 2 cc. of blood, and the coagulation time was determined by the Lee and White method. All tests were performed in a water bath at 37° C. Due

\* Connaught Laboratories—1000 units per 1 cc.

to technical difficulties, the same degree of accuracy could not be realized when working with whole blood as when working with plasma. However, sufficient data were accumulated to demonstrate that the trend of the results was similar. Products that were inactive in plasma were inactive likewise in whole blood. Products that showed a high degree of coagulative potency in plasma were capable of reducing the coagulation time of the specimens of whole blood to  $\frac{1}{2}$  to 3 minutes.

**Results.** The ranges of coagulation time for the saline control specimens, with which the following results may be compared, were:

For *normal plasma*, 90 to 120 seconds.

For *hemophilic plasma*, 400 to 500 seconds.

1. *Thromboplastin Solutions for Local and Oral Administration.* Products 1 to 5 inclusive are solutions of thromboplastin for local or oral use. In all instances, in both normal (Fig. 1) and hemophilic

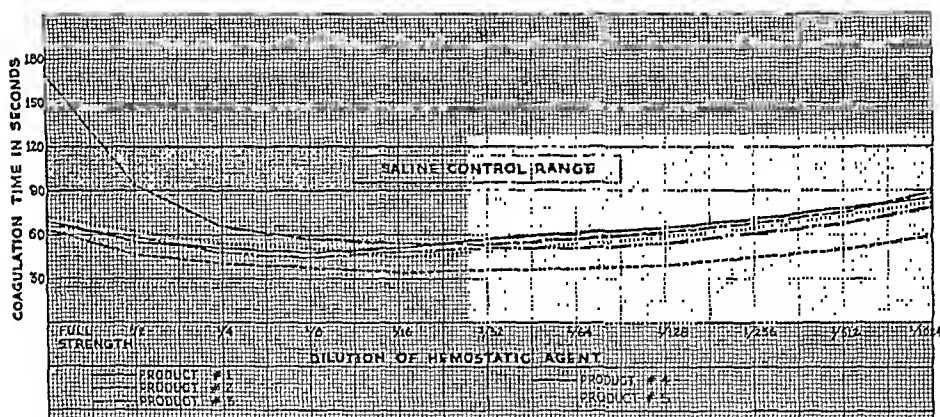


FIG. 1.—The coagulating potency of local thromboplastin solutions tested with normal human plasma.

plasma (Fig. 2), the range of concentrations showing activity was very broad. The shortest coagulation times with *normal plasma* varied between 32 and 52 seconds for the various products. The shortest coagulation times with *hemophilic plasma* varied between 41 and 90 seconds for these same products.

2. *Fibrinogen Solutions for Oral and for Hypodermic Administration.* Products 6 and 9, the preparations of tissue fibrinogen for oral and hypodermic use respectively, were inactive in every concentration in *normal plasma*, and showed only slight potency in high concentrations in *hemophilic plasma*. The coagulation time of the oral product in *hemophilic plasma* was 195 seconds, and of the hypodermic product 120 seconds when the products were used in full strength. Increase in dilution of either product resulted in gradual prolongation of the coagulation time.

3. *Snake Venoms for Local Administration.* (a) *Fer-de-lance* venom. *Fer-de-lance* venom (Product 7) may be obtained in the dry form as a yellow amorphous substance. It is soluble slowly in

0.85% NaCl and when added to the commercial diluent. It is dispensed commercially as a 1 to 5000 solution, and in this form was found to produce a coagulation time of 47 seconds in the  $\frac{1}{4}$  dilution in *normal plasma* (Fig. 4). The coagulation time in *hemophilic plasma* was 57 seconds when the product was used in full strength (Fig. 5). A 1 to 5000 solution of the venom freshly mixed in the commercial diluent in our laboratory gave a coagulation time of 21 seconds in the  $\frac{1}{4}$  dilution in *normal plasma*, and of 31 seconds in

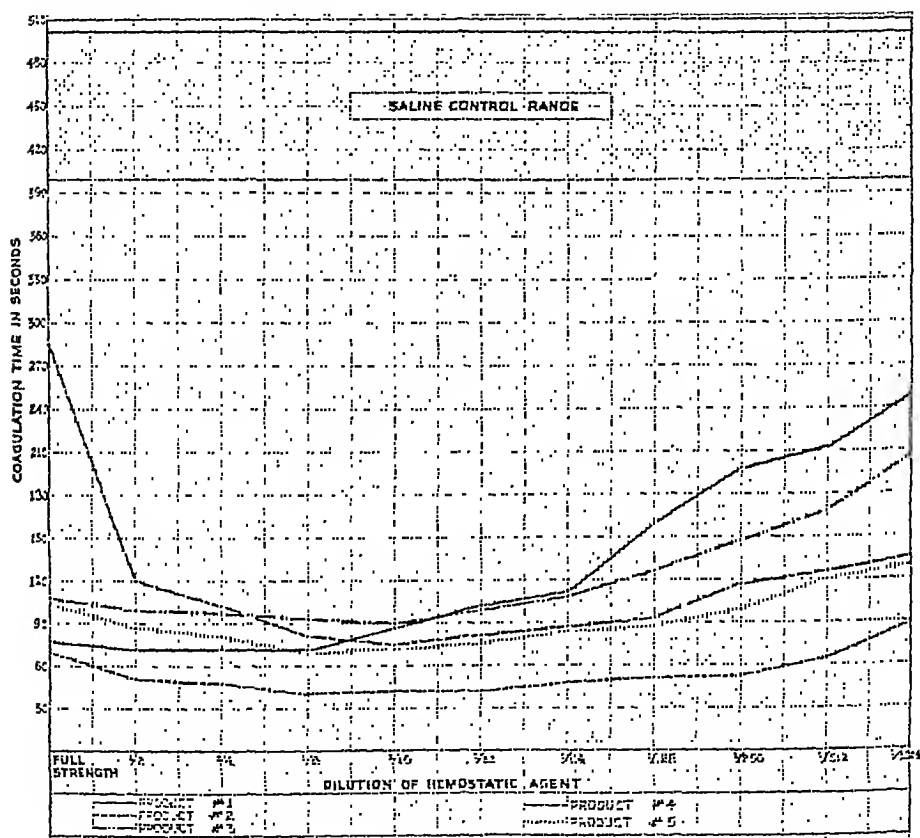


FIG. 2.—The coagulating potency of local thromboplastin solutions tested with hemophilic plasma.

the  $\frac{1}{4}$  dilution in *hemophilic plasma*. A 1 to 5000 solution of the venom in 0.85% NaCl in full strength gave a coagulation time of 12 seconds in either *hemophilic* or *normal plasma*. The commercial diluent in full strength was found to be slightly anticoagulant, prolonging the coagulation time to 170 seconds in *normal plasma*. The anticoagulative action of the commercial diluent and changes due to ageing in solution probably account for the decreased potency of the commercially dispensed solution as compared to venom freshly mixed in 0.85% NaCl.

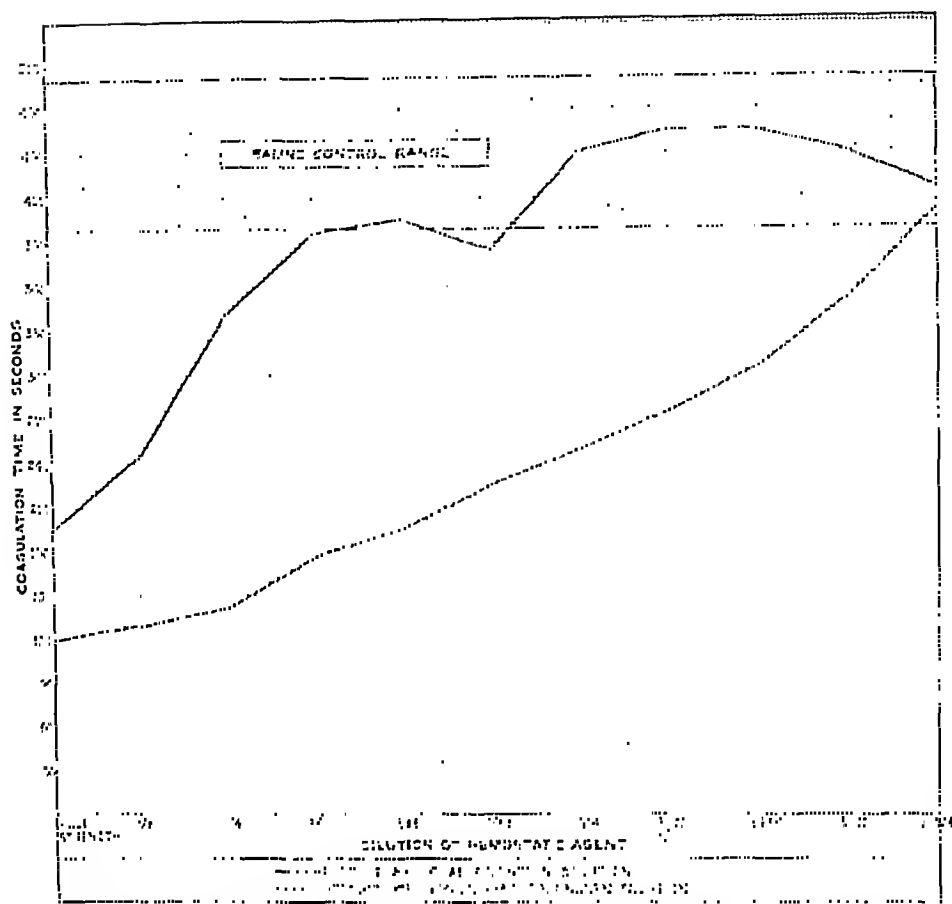


FIG. 3.—The coagulating potency of fibrinogen solutions tested with hemophilic plasma.

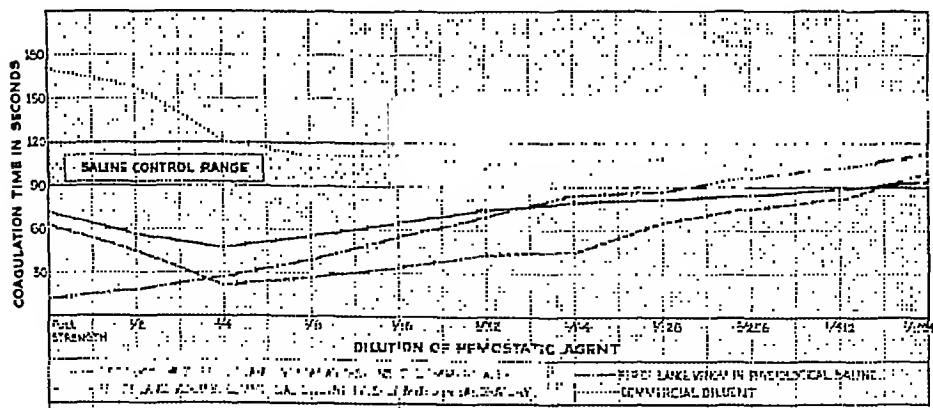


FIG. 4.—The coagulating potency of Fer-de-lance venom tested with normal human plasma.

(b) Russell's viper venom. Dried Russell's viper venom (Product 8) is readily soluble both in the commercial diluent and in 0.85% NaCl. Parallel tests with either diluent gave almost identical results. When the product was used in full strength, the coagulation time was 30 seconds in both *normal* and *hemophilic plasma* (Figs. 6 and 7). In both instances the range of concentrations producing activity was broad.

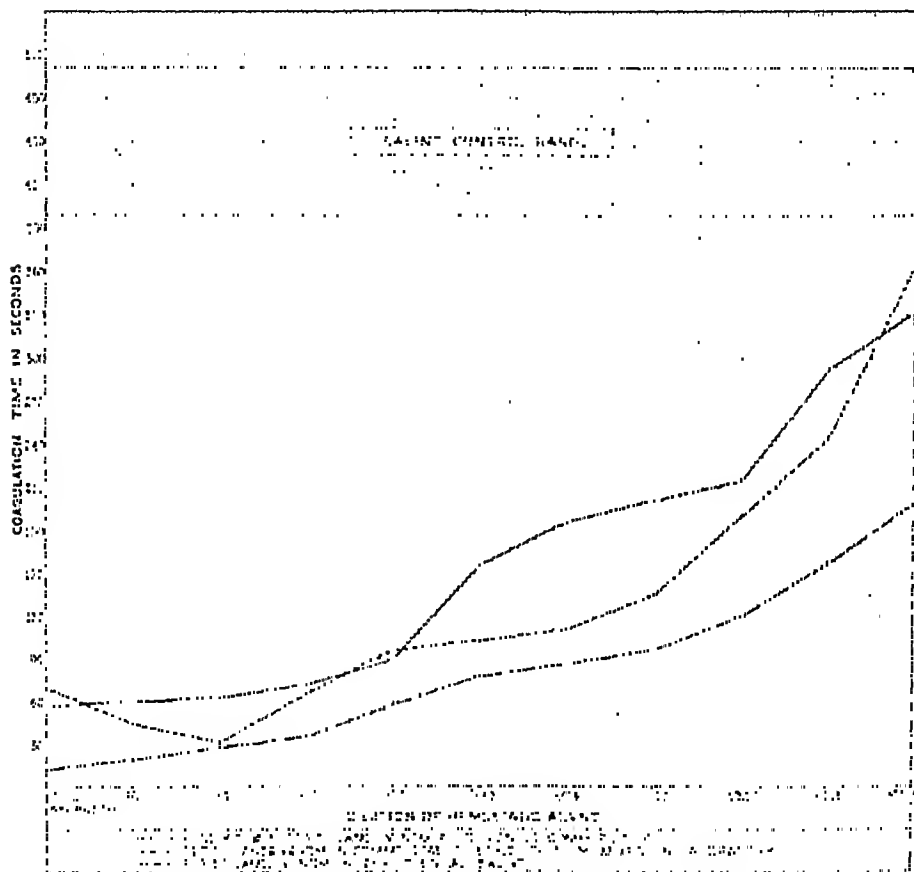


FIG. 5.—The coagulating potency of Fer-de-lance venom tested with hemophilic plasma.

4. *Solutions of Thromboplastin for Hypodermic Administration.* Products 11 to 14 inclusive are either clear, colorless solutions or turbid colloidal suspensions containing a small amount of finely dispersed particulate matter. All of these products were found to be inactive in *normal plasma*. Products 11 and 13 were studied also in *hemophilic plasma* and found to be inactive. Product 10 is a turbid colloidal suspension containing gross tissue particles. It was found to produce a coagulation time of 54 seconds in the  $\frac{1}{4}$  and  $\frac{1}{8}$  dilutions in *normal plasma*, and of 64 seconds in *hemophilic plasma*.

5. *Bovine Blood Derivative for Local, Oral or Hypodermic Administration.* There was no coagulative activity in any concentration of this product (No. 15) when used either in normal or hemophilic plasma.

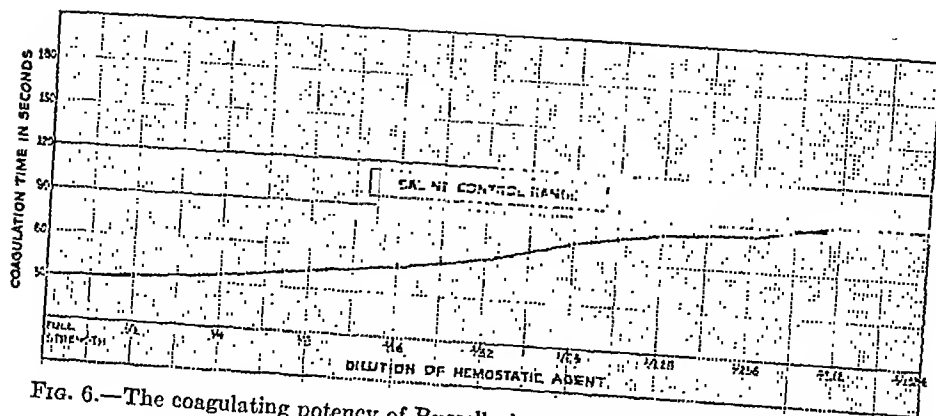


Fig. 6.—The coagulating potency of Russell viper venom tested with normal human plasma.

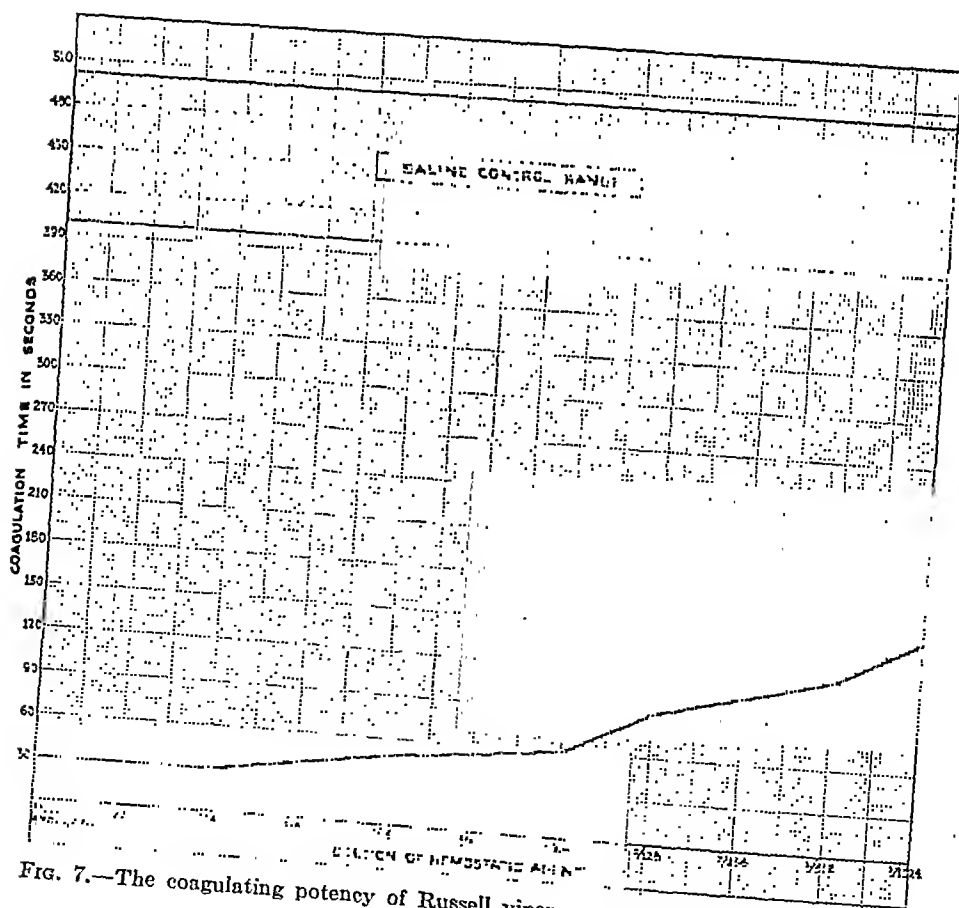


Fig. 7.—The coagulating potency of Russell viper venom tested with hemophilic plasma.

6. *Horse Sera.* These sera, Products 16 and 17, were inactive in *normal plasma*. The effect of Product 17 on *hemophilic plasma* was studied. There was slight coagulative activity in high concentrations when used in full strength, giving a coagulation time of 154 seconds.

7. *Solutions of Thromboplastin for Local Use Derived From the Brains of a Variety of Species.* Local solutions of thromboplastin derived from the brains of the horse, dog, rabbit, sheep and guinea-pig were made by the manufacturer of Product 2 (a thromboplastin solution for local use derived from calf brain). The shortest coagulation times in *normal plasma* for the various products were as follows: horse, 24 seconds; dog, 25 seconds; calf, 34 seconds; rabbit, 37 seconds; sheep, 90 seconds; and guinea-pig, 113 seconds. In *hemophilic plasma* the shortest coagulation times were: horse, 26 seconds; dog, 29 seconds; calf, 41 seconds; rabbit, 36 seconds; sheep, 135 seconds; and guinea-pig, 395 seconds (Figs. 8 and 9).

The products derived from horse, dog, calf and rabbit brain maintained their coagulative activity throughout a very wide range of concentrations. The solutions derived from sheep and guinea-pig brains were highly anticoagulative in high concentrations, and in no concentration was any coagulative activity demonstrable in *normal plasma*. In *hemophilic plasma*, the product derived from sheep brain, upon dilution, showed moderate coagulative activity, while that derived from guinea-pig was inactive.

8. *Solutions of Thromboplastin for Hypodermic Use Derived From the Brains of a Variety of Species.* Hypodermic thromboplastin solutions derived from the brains of the horse, dog, rabbit, sheep and guinea-pig were made by the manufacturer of Product 12 (a solution of thromboplastin for hypodermic use derived from calf brain). These solutions were uniformly inactive in both *normal* and *hemophilic plasma*.

**Comment.** All of the commercial solutions of thromboplastin for local or oral use are made from bovine brain. They all possess a high degree of coagulative potency. However, in view of our findings, it is apparent that the brain of the dog or horse is a better source of material for this type of preparation. The solutions of thromboplastin suitable for hypodermic administration are uniformly inactive. It is stated that these solutions are produced by dilution, filtration and deproteinization of the crude material used in the preparation of solutions of thromboplastin for local use. Contrary to the popular conception, this is not a concentration or extraction of the active coagulative elements contained in the crude emulsions. It is possible, by centrifugalization of crude tissue emulsions, to obtain turbid colloidal suspensions free of particulate matter that are as active through as wide a range of concentrations as are the crude tissue emulsions. It is as yet impossible, however, to extract, concentrate or refine the active component contained in these solutions.

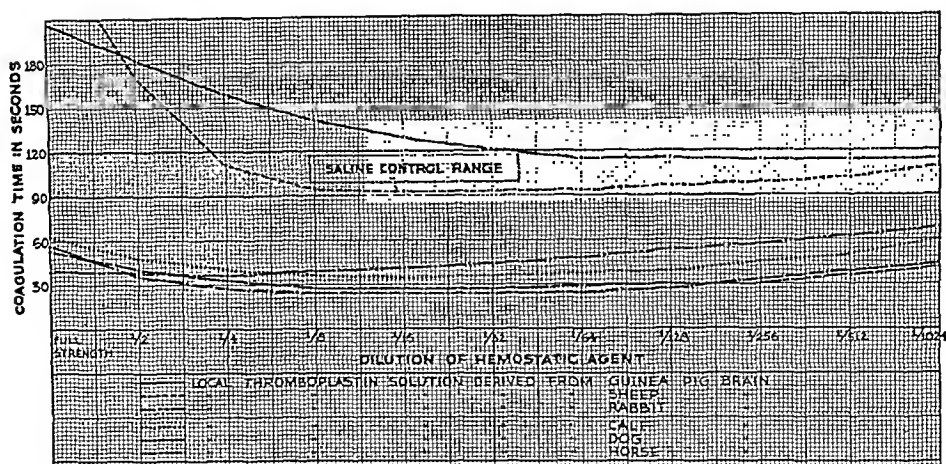


FIG. 8.—The coagulating potency of local thromboplastin solutions derived from the brains of a variety of species tested with normal human plasma.

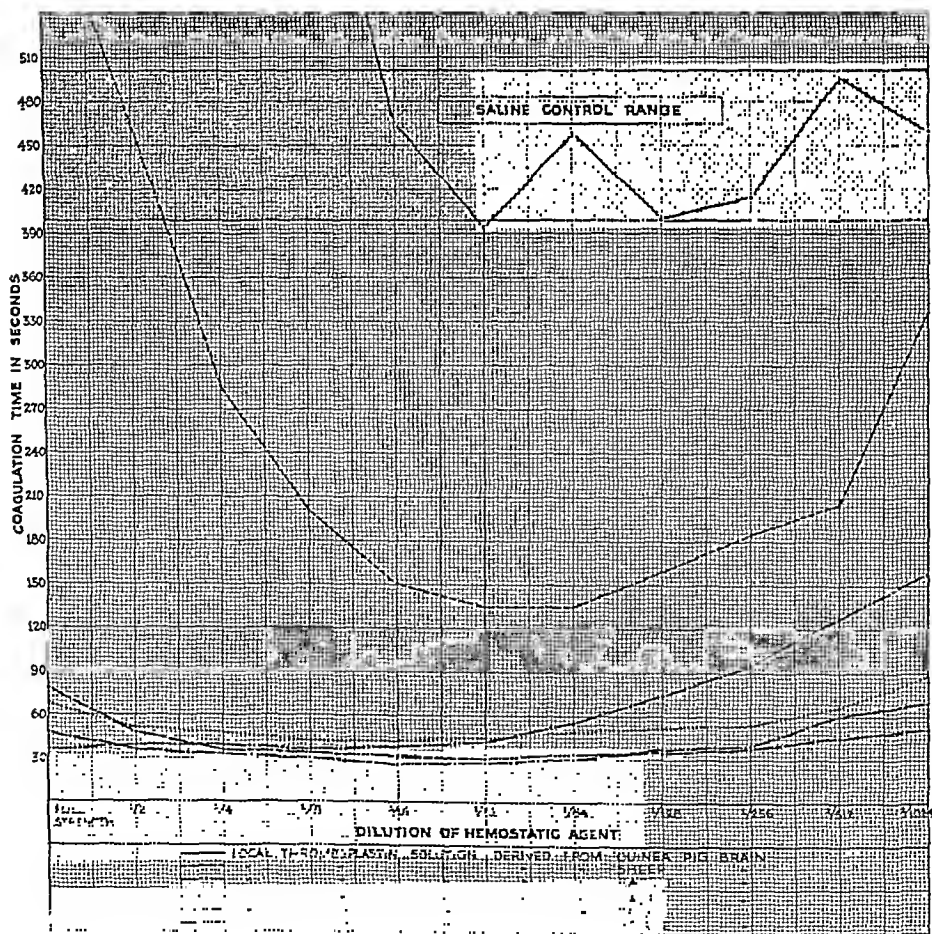


FIG. 9.—The coagulating potency of local thromboplastin solutions derived from the brains of a variety of species tested with hemophilic plasma.



Quick<sup>11</sup> has shown that the coagulative potency of both the extracted material and the residue after extraction with lipoid solvents is markedly diminished. For this reason cephalin, which is an ether extract of brain tissue, is inferior as a coagulant to the crude aqueous emulsion of brain. Recently Chargaff<sup>2</sup> has prepared a highly anticoagulative substance from brain tissue by extraction with lipoid solvents.

The fibrinogen products are relatively impotent. They must depend for their action upon a small amount of cephalin and traces of thromboplastin carried down with the globulin fraction in the preparation of fibrinogen. Fibrinogen itself has been shown to be inactive in promoting blood coagulation. Similarly, the content of thromboplastin in the two sera above mentioned is too small to be of any significance in promoting blood coagulation. The derivative of bovine blood, although it is stated to be an extract of platelets, retains none of the coagulative properties of platelets. It is totally inactive. With respect to all of these products derived from blood or tissue, it is of no intrinsic value whether the material be derived from brain, from lung, from testicular tissue, from serum, or from whole blood. The degree of its ability to supply a coagulative principle is of paramount importance.

The two snake venoms possess a degree of coagulative activity roughly comparable to that of the solutions of thromboplastin for local use.

Of the claims made for the various products, those such as the following are frankly misleading:

Fibrinogen solution: "The clotting time is reduced 90 per cent."

Horse serum: "The coagulant potency is fifteen times that of normal horse serum."

Thromboplastin solution: "(It) is standardized to coagulate citrated or oxalated plasma in two minutes or less, a clotting time very close to the shortest possible reaction."

Thromboplastin solution: "(It) accelerates the clotting time of blood from three to seven times more than any other substance."

Fer-de-lance venom: "Judging by the greatest dilution in which each of these materials is equally effective, (it) has a coagulating power 500 times greater than 10 per cent thromboplastin."

In order to state that a substance hastens coagulation of blood, one should be able to demonstrate this action *in vitro*. Yet 9 of the 17 products studied were found to be practically inactive (Figs. 10 and 11). The only substances that were significantly active were crude tissue emulsions and snake venoms, products suitable exclusively for local or oral use. Products suitable for parenteral administration had no significant potency. In 1919 Hanzlik and Weidenthal showed that Products 15 and 17 had no coagulative action, yet these products are still manufactured and used. The need for potent hemostatics is recognized. The use of

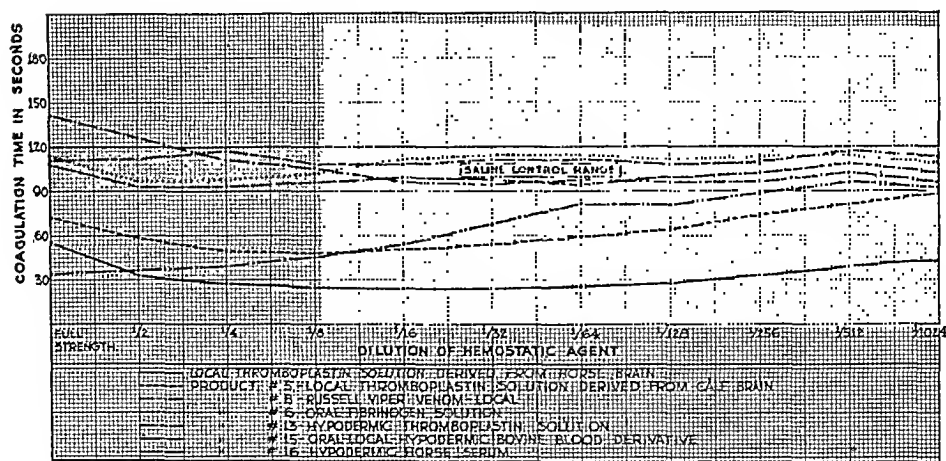


FIG. 10.—The coagulating potency of various types of commercial hemostatic agents tested with normal human plasma.

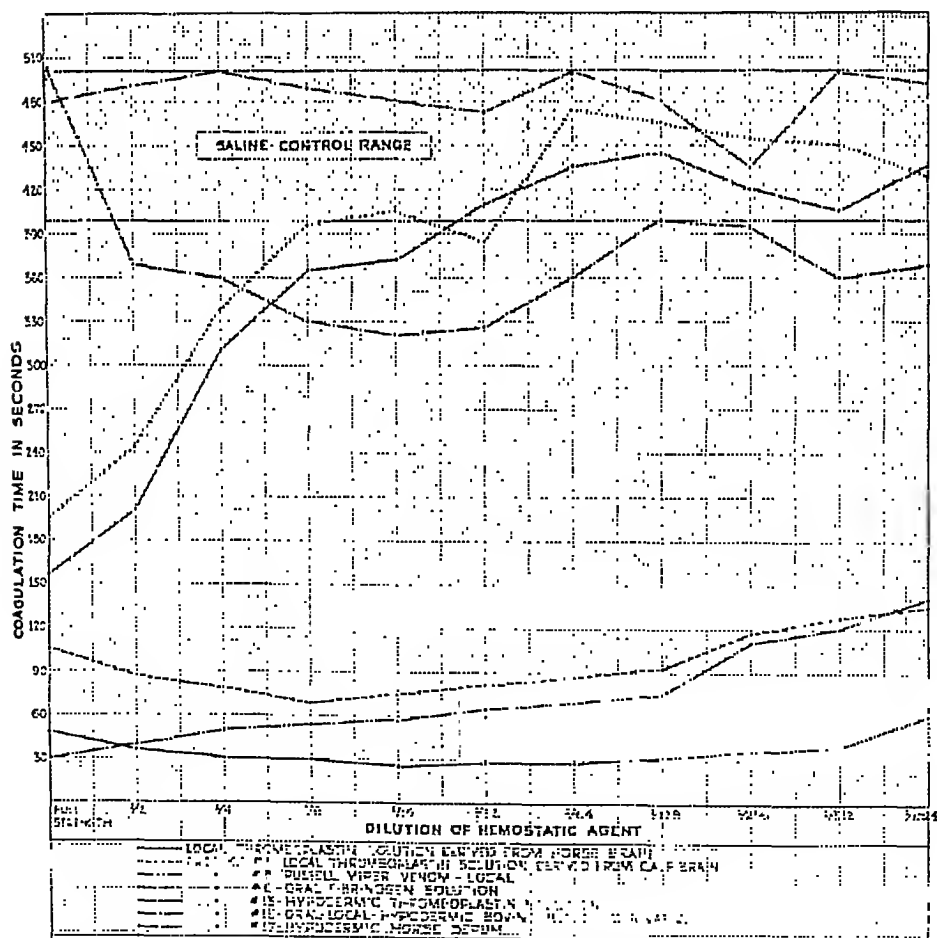


FIG. 11.—The coagulating potency of various types of commercial hemostatic agents tested with hemophilic plasma.

impotent agents in the forlorn attempt to "do something" when confronted with the problem of the bleeding patient should be discouraged.

**Summary.** The coagulative potency of 17 commercially available products and of 10 solutions of thromboplastin obtained from the brains of various species were tested for their ability to hasten coagulation of the blood *in vitro*.

Of the 17 commercially available products, 9 were found to be practically inactive. The only products found to be significantly active were those suitable for local or oral use.

We acknowledge indebtedness to various manufacturers for generous supplies of the products used in this study.

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### TRAUMATIC COMPLICATIONS IN PERIPHERAL VASCULAR DISEASE.

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DURING the past 15 years, a great fund of information has accumulated and a considerable awareness has developed on the subject of peripheral vascular disease. Nevertheless, about the same number of patients afflicted with such disease continue to be seen and they continue to die at about the same rate as formerly. Although this situation is rather discouraging, one hopeful but as yet superficially explored field remains for investigation. That is the field of prophylaxis. It is our purpose to call attention to one practical and immediately applicable aspect of prophylaxis; namely, the elimination of trauma as a factor in production of open lesions in extremities afflicted with reduced circulation. While taking

histories of patients so afflicted we were impressed with the frequency of antecedent injury. A brief review of the altered physiology of extremities with diminished circulation will enable us to understand better what constitutes trauma to them.

The skin of the extremities constitutes about 60% of the body surface in man. Body temperature in the normal subject is mostly controlled by a delicate adjustment of circulation to this large skin surface in response to variations of internal and environmental temperatures. This mechanism is the familiar one of vaso-constriction in response to cold and vasodilatation in response to heat. Moreover, as a corollary to circulatory regulation of body temperature an efficient circulation has two other functions: in cold environments it warms the tissues of the limbs; in high environmental temperatures, on the other hand, it acts as a cooling system for these parts in essentially the same manner as does the cooling system of an automobile engine. But the striking result of occlusive arterial disease is to produce a relatively rigid, non-labile circulation. Such an impaired blood flow obviously cannot maintain coolness in relatively high temperatures and cannot maintain adequate warmth in low temperatures. Consequently excesses of cold or of heat easily handled by a normal circulation may be lethal to tissue of an extremity afflicted with a rigid circulation. Hence the frequency in such extremities of frost-bite from mild exposure to cold and of burns from ordinarily harmless therapeutic heat.

A simple experiment will illustrate this point. The subject was a male Greek of 53 suffering from thrombo-angiitis obliterans of both extremities. He complained of pain in the feet at night and of intermittent claudication in the right calf on walking four or five blocks. Moderate diminution of circulation was present on the left; marked diminution on the right (Fig. 1). In the experiment both feet were enclosed in a heating chamber. Observations of environmental temperatures and of skin temperatures of the great toes were taken at intervals. At room temperature the right great toe was slightly cooler than the left as one would expect. As environmental temperature increased the temperature of both great toes rose together for a time, but later the temperature of the right great toe suddenly rose above that of the left. At the end of 50 minutes in an environmental temperature of only 104° F. pain in the right foot necessitated ending the test.

Another point in regard to heat should be understood. Freeman<sup>3,4</sup> has shown that temperatures above normal in the extremities increase local tissue metabolism. In other words, warmed tissues require increased circulation to bring more oxygen and food and they produce more waste products to be carried away. But a rigid circulation can not meet such a demand. Consequently, heat accelerates death of tissue poorly supplied with blood. It is not strange, therefore, that ordinary therapeutic heat, so successfully

used for various aches and pains and for inflammatory processes in normal individuals, may result in serious burns and rapid extension of necrosis when employed on patients with obliterative vas-

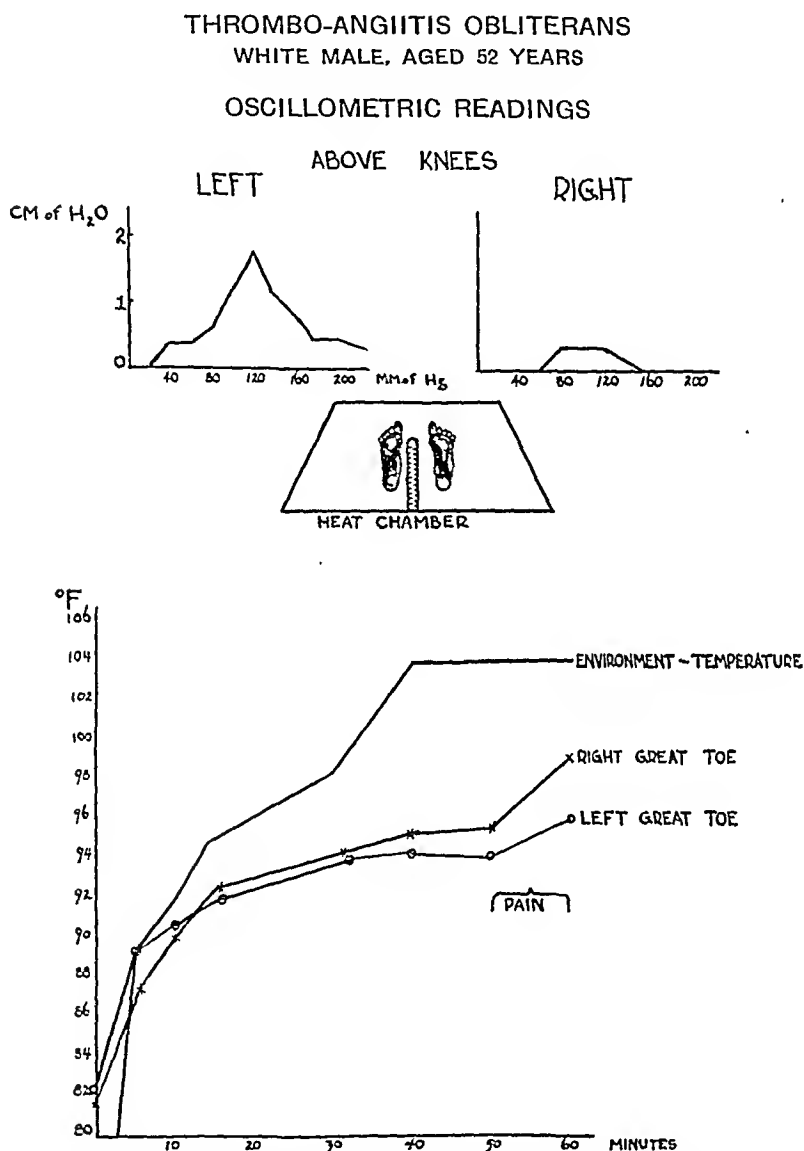


FIG. 1.—Effects of high environmental temperatures on extremities with normal and with diminished arterial circulation.

ular disease. An inflammatory process also increases local metabolism, which accounts for the rapidly advancing gangrene frequently seen when an inflammatory process involves a poorly nourished extremity.

The increased vulnerability of limbs with deficient circulation is further increased by the rapid loss of function of completely or relatively ischemic sensory nerves.<sup>7</sup> Persons with ischemic extremities are very apt to be unaware of temperature excesses which are producing injury. It is not unusual for patients using hot soaks of feet and legs to relieve the pain due to limited circulation to sustain severe burns without experiencing the pain which usually occurs with such burning.

In résumé, physiologic responses to thermal stimuli are altered in three ways in ischemic limbs: the warming and cooling functions of the circulation are impaired; capacity to cope with increased metabolism of warmed or inflamed tissues is diminished; sensibility to painful stimuli is lessened.

Consider mechanical types of injury. It suffices to mention such accidental injuries as stubbing the toe and bruising or crushing a toe or foot. The onset of many open lesions begin with a blister or a corn raised by tight or ill fitting shoes. In a large number of patients open lesions follow a visit to a chiropodist or to a physician for treatment of corns and of real or alleged ingrowing toenails. Pressure is also a frequent source of injury. In the words of Sir Thomas Lewis,<sup>7</sup> "Much lower pressure than that required to collapse the main artery will, when exerted directly upon the muscle itself, collapse its capillaries and completely arrest the blood flow to it. A pressure of 50 or 60 mm. Hg upon skin is known to stop all blood flow to it." He further states that ischemic muscle dies in 6 to 8 hours, nerve in 12 to 20 hours and skin in 24 to 36 hours. One can readily understand why relatively minor degrees of pressure on poorly nourished extremities may produce rapid and extensive necrosis.

Even improper position of the limb may be injurious. Reid<sup>10</sup> showed that optimum circulation occurs in an extremity resting 6 or 8 inches below the heart's level. Yet most patients are advised to elevate their legs on several pillows. The patient, on the other hand, in his attempt to escape from pain is frequently seen with a cold blue foot hanging out of bed.

Strong chemicals frequently injure undernourished extremities. Chemicals powerful enough to act as germicides may be equally deadly to devitalized tissue. Because circulation in these limbs is usually not adequate to sustain an inflammatory process, application of chemicals to produce counter-irritation, essentially an inflammatory process, is dangerous. Chemicals such as iodine, salicylic acid, phenol and other germicides and counter irritants should be used with great caution in peripheral vascular disease.

**Clinical Material.** Tables 1 and 2 present clinical data on 40 patients who were admitted to the hospital for peripheral vascular disease during a 6-month period. That such patients constitute a serious medical and economic problem is attested by the following

facts. In a hospital in which the average patient's stay is 12 days, these averaged 55 days. Based on the United Hospital Fund (New York) the average cost for each patient was \$303; \$12,122 for the group. Moreover, during the same period in which 40 patients were admitted for peripheral vascular disease, only 9 were admitted for perforated peptic and duodenal ulcers and only 33 were operated for gall bladder disease. Furthermore, of 52 patients with peripheral vascular disease who entered with open lesions more than half required amputation and more than half of those having amputa-

TABLE 1.—PATIENTS ADMITTED PRIMARILY FOR PERIPHERAL VASCULAR DISEASE, FEBRUARY 1 TO AUGUST 1, 1938.

	Male 31	Female 9	Total 40			
Age distribution:						
Decade . . . . .	3d	4th	5th	6th	7th	8th
Male . . . . .	1	1	4	9	12	4
Female . . . . .	..	1	2	1	3	2
Total . . . . .	1	2	6	10	15	6
Diseases:						
Thromboangiitis obliterans . . . . .						7
Occlusive arteriosclerosis . . . . .						10
Occlusive arteriosclerosis with diabetes . . . . .						19
Arterial embolus . . . . .						4
Mortality:						
				No.	Per cent.	
Patients who entered the hospital with open lesions . . . . .				32		
Amputations on these patients . . . . .				17	53	
Deaths following amputation . . . . .				9	53	
Deaths not following surgery . . . . .				1		
Total deaths in 40 patients . . . . .				10	25	
Deaths in those who entered with open lesions . . . . .				10	31	

tions died. In other words, a person afflicted with peripheral vascular disease, who develops an open lesion, is immediately faced with a prolonged and painful disability and about a 30% chance of dying. These figures agree closely with those of other writers.<sup>6</sup> Even if these patients survive amputation, only about 10% are ever economically rehabilitated.<sup>6</sup> Obviously development of open lesions in vascular disease of the extremities is an occurrence of dire import.

Table 2 shows that trauma is apparently a major factor in production and aggravation of open lesions. Of 32 patients from whom a satisfactory history was obtainable more than half of them had sustained one or more types of injury. The majority of these injuries resulted from some form of ill-advised therapy. That injury, as well as diminished circulation, is often necessary to produce open lesions is indicated by the fact that in 13 of these patients circulation was equally poor in both extremities and that in 7 the lesion was actually on the limb with distinctly better circulation. There were 37 instances of injury in 21 patients. In only 13 instances was self treatment or an accident the source of injury. The remain-

ing 24 instances of trauma occurred through the advice or at the hands of some professional attendant; 53% of the injuries were occasioned by medical attendants.

TABLE 2.—TRAUMA.

	No.	Per cent.
History of trauma . . . . .	21	52
No history of trauma . . . . .	11	27
Unsatisfactory history . . . . .	8	20
	<hr/> 40	
Lesions:		
Gangrene . . . . .	20	
Dry . . . . .	11	
Infected . . . . .	9	
Indolent ulcer . . . . .	7	
Cellulitis or osteomyelitis . . . . .	5	
	<hr/> 32	
Total with open lesions . . . . .	32	
No open lesions . . . . .	8	
Syphilitic . . . . .	6	
Site of lesions:*		
Lesion on extremity with poorer circulation . . . . .	12	
Lesion on extremity with better circulation . . . . .	7	
Circulation of both extremities essentially same . . . . .	13	
Those responsible for the trauma:		
Patient . . . . .	13	35
Chiropodist . . . . .	4	11
Family physician . . . . .	18	48
Hospital staff . . . . .	2	5
	<hr/> 37	

## Types of injury:

1. *Mechanical*: 17 instances.

## A. Pressure.

## 1. Tight shoes.

## 2. Casts applied for "arthritis," "varicose veins," etc.

## 3. Pressure of heel on bed with resulting gangrene.

## B. Local operations on corns or nails.

## C. Accidental injuries such as stubbing toe or having it stepped on.

2. *Thermal*: 16 instances.

## A. Cold. Usually exposure. Occasionally, too enthusiastic use of contrast baths.

## B. Hot soaks. Usually in strong solutions of Epsom salts ("as hot as you can stand it").

## C. Baking lamps and infra red lamps.

## D. Diathermy and short wave.

3. *Chemical*: 4 instances. Iodine, salicylic acid and phenol ointments. Vaseline gauze to dry gangrene. Use of strong chemicals for epidermatophytosis.

\* Measured by exercise and blanching test, venous filling time, oscillometry and histamine readings.<sup>1,2,5,9,11a,b</sup>

**Discussion.** The idea unfortunately still persists that specialized knowledge and considerable elaborate and expensive apparatus are required for diagnosis of vascular diseases of the extremities. The contrary, however, is true. In a previous publication<sup>8</sup> one of us showed that accurate diagnosis of circulatory status can be made at the bedside without apparatus of any kind and with only the familiar methods of inspection and palpation and two simple tests.<sup>1,11b</sup>



Failure to recognize deficiency of circulation is often the starting point of mischief. Accurate diagnosis and early recognition of the vulnerability to trauma of these patients is their best safeguard. Having recognized diminished circulation of the extremities the physician must keep clearly in mind those measures to be avoided and those to be carried out to prevent onset of open lesions. Properly fitting shoes, light woolen socks, scrupulous cleansing of the feet with tepid water and non-caustic soap, gentle drying with soft towels; avoidance of cold and wet, meticulous care of the nails, corns and callouses, adequate rest, supervised exercise and the general medical measures especially adapted to the case—all these are requisite. Indiscriminate applications of wet dressings, whether hot or cold, use of moist or dry heat and employment of strong chemicals cannot be tolerated. Avoid pressure on the heel and pressure on the popliteal space by bunched-up pillows. Pressure from bed clothes should be eliminated. Body temperature of the limb may best be maintained by warm clothing and by wrapping the entire foot and leg loosely in cotton wool. Contrast baths may do more harm than good. Dry dressings or none at all are usually preferable. Maceration of tissue by vaseline gauze or by other occlusive dressing should be avoided.

Surgical trauma, likewise, should be reduced to a minimum. Surgery, when indicated, must not be delayed and it must be adequate. Radical surgery is usually the most conservative, because few of these patients can tolerate repeated surgical insults, whereas many will survive a single, well planned attack. If amputation is necessary, it should be performed at a level at which risk of contamination is least and at which viability of tissue is most promising. Scrupulous skin sterilization, careful draping, elimination of tourniquets, clean quick incisions with sharp scalpels without beveling skin edges, gentle retraction, no clamping of skin, no interruption of essential blood supply by separation of skin from underlying tissue in fashioning flaps, nice hemostasis without gross clamping of tissue, fine ligatures throughout except where heavier material is essential, no suturing of muscle, judicious apposition of fascial edges, accurate closing of skin without tension and finally, a well applied dressing without drainage—all are requisite. Such precautions entail a minimum of operative trauma. The operative site may usually be forgotten until healing has occurred. Even after amputation the remaining limbs of these patients are still subject to the effects of trauma and must be carefully safeguarded.

**Summary and Conclusions.** 1. Because of the altered physiology of extremities afflicted with obliterating arterial diseases many ordinary therapeutic measures cause injury and produce open lesions in such limbs.

2. Investigation of 40 patients with peripheral vascular disease showed that more than half of them suffered one or more injuries in the course of ill advised attempts at treatment.

3. Trauma appears to be the most frequent cause of open lesions in extremities with poor arterial blood supply. Types of injury have been discussed.

4. Because development of open lesions on poorly nourished limbs entails great economic loss, prolonged morbidity and a high death rate, every effort should be made to eliminate trauma in patients with peripheral vascular disease.

5. This object can be accomplished only by a widespread and a persistent campaign of education among physicians.

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### ELECTROCARDIOGRAPHIC STUDIES IN METRAZOL SHOCK THERAPY.

#### REPORT OF ELECTROCARDIOGRAPHIC FINDINGS OBTAINED IN THE TREATMENT OF 50 SCHIZOPHRENIC PATIENTS WITH CONVULSIVE SHOCK INDUCED BY METRAZOL.

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SINCE the introduction of metrazol shock therapy in the field of the functional psychoses, much attention has been devoted to the changes in the bodily economy induced by the large doses of this potent drug which are required to produce the therapeutically desired grand mal seizures. Particularly thoughtful workers have been concerned with the possibility of serious or even fatal damage to the brain, heart, lungs, kidneys, skeletal structures, and so on, as a result of this therapy.

That disastrous effects<sup>2,3</sup> on the cardiovascular system can follow the incautious administration of this drastic therapy, there is little doubt. Thus, von Angyal and Gyarfas<sup>1</sup> record a fatal case in which

aortic stenosis was found to be present at postmortem. Hayman and Brody<sup>4</sup> also report a fatal case in which a preëxistent chronic endocarditis was found at autopsy.

Such instances emphasize the danger of convulsive doses of metrazol in patients with damaged hearts. This paper is the outgrowth of an effort to determine the possible untoward effects of metrazol shock therapy upon the cardiovascular system of young subjects manifesting no evidence of impaired cardiovascular system before the institution of therapy. In particular, we are concerned here with such possible ill effects insofar as they can be detected by electrocardiographic studies.<sup>7,8</sup> Collateral phenomena such as roentgenologic studies of the cardiovascular system, blood pressure, venous pressure, and so on, are not included in this report.

**Material and Method.** The material for this work was taken from electrocardiographic studies on schizophrenic subjects undergoing metrazol shock therapy at this hospital. All patients considered for this treatment underwent as routine work-up a careful clinical examination of the cardiovascular system, Roentgen ray of the chest and an electrocardiogram besides the other usual tests. In addition, each patient received at the conclusion of the therapy a clinical check-up of the cardiovascular status and a second electrocardiogram.

Patients selected for this study were all diagnosed as suffering from schizophrenia. There were 25 males and 25 females in the present series of 50 patients. The oldest patient was 44; the youngest 19 years (average age, 26 years). Patients presenting any cardiovascular abnormalities either on clinical, roentgenologic, or electrocardiographic examination were considered unsuitable for therapy and hence excluded from this study. Treatment consisted of intravenous injections of 10% aqueous solution of metrazol (pentamethylenetetrazol) 3 times a week according to the technique developed by von Meduna.<sup>6</sup> The duration of therapy lasted from 4 to 16 weeks (average, 8 weeks). The total amount of metrazol solution injected was from 64 to 469 cc. (average, 196 cc.). The number of grand mal seizures varied from 10 to 40 (average, 21).

The electrocardiograms for this study were analyzed for rate and rhythm, *P*, *Q*, *R*, *S*, and *T* waves, *P-R* and *S-T* segments. The electrocardiogram before the institution of therapy was compared with the one taken after the completion of the treatment.

**Results.** In this series of 100 electrocardiograms (50 before and 50 after treatment), the rhythm in every instance was of a sinus type. Thirty-one (62%) of the cases showed an increase of rate after treatment (3 [6%] of the cases showed a decrease in rate after therapy). Average rate before treatment was 85; after treatment, 115. The increase in rate following therapy was attributed to emotional factors, since it was observed that those patients who manifested nervousness, anxiety, fear and apprehension while the electrocardiogram was being taken frequently showed tachycardia. This has been commonly observed following metrazol shock treatment, since many patients evidently confused the electrocardiogram with the feared metrazol injection.

Apparently related to this phenomenon was the shortening of

the *S-T* segment (interval) which was observed in 23 (46%) of cases following therapy (as compared with electrocardiogram before treatment). In every instance in which this phenomenon was observed, the rate was found to have increased after therapy. Four of these 23 patients likewise showed a shortened *P-R* interval. We regard this shortened *S-T* interval, and occasional shortening of *P-R* interval, as merely a physiologic concomitant of the increased rate.

There were no significant changes in *P* waves or *QRS* complexes in our entire series. The *T* waves in 48 (96%) of our series likewise showed nothing significant. In 2 patients, however, interesting changes were observed as seen below.

CASE 1.—G. M., a 21-year-old female had a negative electrocardiogram before institution of therapy. She received a total of 310 cc. of metrazol given in 40 injections, 30 of which resulted in grand mal seizures. The largest single dose was 9 cc. Her therapy was terminated on March 3, 1939. At no time during or after treatment were any cardiovascular abnormalities detected clinically. However, routine electrocardiogram on March 9, 1939, showed inversion of *T*<sub>2</sub> and *T*<sub>3</sub>, with depression of *S-T*<sub>2</sub>. The *T* waves were of cove-plane type and suggested coronary changes. On April 5, 1939, a similar record was obtained. On April 10, 1939, however, without any therapy of any sort, these changes disappeared and a normal electrocardiogram was obtained. Furthermore, electrocardiograms on April 18 and 25, 1939, showed upright *T* waves in all leads and negative electrocardiograms.

CASE 2.—S. L., a 21-year-old male with negative electrocardiogram before therapy was given a total of 189.5 cc. of metrazol in 25 injections. He had 20 seizures of grand mal type. The largest single dose was 10 cc. His last injection was given on April 26, 1939. An electrocardiogram on April 28 revealed inverted *T*<sub>2</sub> and *T*<sub>3</sub> and again was considered as suggesting coronary disease. It was suggested that anoxemia<sup>5</sup> might account for these changes. Acting upon this suggestion, the patient was given 100% oxygen by inhalation (with a Gwathmey anesthesia machine) for 15 minutes. Thirty minutes later, an electrocardiogram was taken and revealed that most of the *T* waves in Leads 2 and 3 were upright. On May 19, 1939, the *T* waves were still upright and electrocardiogram was normal in appearance.

**Summary.** 1. Electrocardiographic tracings taken before and after metrazol shock therapy administered to young healthy adults revealed no significant changes of a permanent nature.

2. An increase in heart rate is frequently observed following therapy. This we believe is due to emotional factors rather than to the metrazol injections *per se*. Shortening of *S-T* (and less commonly of *P-R*) intervals is also commonly observed. This, in our opinion, is associated with the increased rate.

3. Inversion of *T* waves in Leads 2 and 3 following therapy occurs in isolated instances. These changes are transient in nature. The mechanism of these changes is somewhat obscure, although they are possibly correlated with anoxemia. This requires further investigation.

4. We wish to emphasize again the need for careful check-up of the physical condition of patients who are being considered for

metrazol therapy. In making such investigations of the physical status of these patients, an electrocardiogram is a valuable adjunct.

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### CHLOROFORM LIVER INJURY INCREASES AS PROTEIN STORES DECREASE.

#### STUDIES IN NITROGEN METABOLISM IN THESE DOGS.

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LIVER injury due to chloroform anesthesia increases in degree as the protein stores are depleted in the liver and body tissues. This is the theme of the experiments tabulated below. Clinicians as well as investigators have a legitimate interest in these observations owing to the unfortunate fact that chloroform is still used as an anesthetic in this country and abroad. If surgeons and obstetricians will persist in the use of this dangerous drug (chloroform) alone or combined with other anesthetics, at least they should realize that the toxicity of chloroform increases as the protein stores are depleted by fasting, intestinal disturbances, bleeding, dietary limitations or even infection.

The normal *well-fed* healthy dog will tolerate an *hour* of surgical chloroform anesthesia with little evidence of severe liver injury. The normal dog *fasted for 3 days* preceding an hour of chloroform anesthesia will always show well marked hyaline central necrosis of the liver, sharp lowering of the fibrinogen and prothrombin levels in the blood, definite increase in bile pigment in blood plasma and urine, large increase in urinary nitrogen and definite clinical intoxication. This is a uniform reaction which can be demonstrated

over and over again, the central liver necrosis involving usually 50 to 70% of the liver cells in each lobule. Occasionally the injury will be severe enough to cause death in 2 to 4 days: "delayed chloroform poisoning."

But when the dog is *depleted of its store of proteins* by long continued low-protein diets with or without bleeding or by plasmapheresis<sup>9</sup> (bleeding and return of washed red cells in saline), we see that the liver is very sensitive to chloroform poisoning (Table 1). These *protein depleted dogs* (normal in all other respects) are scarcely able to tolerate 12 minutes of light chloroform anesthesia and 20 minutes will be fatal in the great majority of cases.

There is every reason to suppose that human beings react like these dogs and under certain conditions may be hypersensitive to chloroform anesthesia. In fact, many cases of fatal chloroform poisoning have been observed and some reported in recent years. In our opinion it would be folly to subject to short chloroform anesthesia human patients who have been vomiting for long periods or who are in a state of inanition due to diet or infection. Young animals and presumably children are somewhat more susceptible than adults.

**Methods.** All dogs used in these experiments were active, healthy adults. As indicated in detail in the individual protocols, the dogs' reserve stores of protein were depleted by bleeding and diet, or by diet alone, or by plasmapheresis. Before starting these procedures the dogs' plasma protein levels were normal (6 to 6.5 gm.%). The constant drain on body protein stores extending over a period of 4 to 7 weeks, finally results in a lowered plasma protein level. A plasma protein level of 4 to 5 gm.% for at least 1 week before the chloroform anesthesia and throughout the metabolism studies was taken to indicate a rather severe depletion of reserve protein stores.

During the metabolism experiments the dogs were kept in the laboratory in galvanized iron metabolism cages. The urine was collected under toluene and preserved with toluene and refrigeration. Each period of 24 or 48 hours was terminated by catheterization and rinsing of the bladder with water. Urine analyses were made on the specimens of each period for the following constituents: Total nitrogen by macro-Kjeldahl, ammonia and urea nitrogen by aëration after urease treatment, creatine and creatinine by the methods of Folin, and uric acid by the method of Morris and MacLeod. Blood samples were drawn from the external jugular vein with 1.4% sodium oxalate used as anticoagulant. Plasma protein determinations were carried out by macro-Kjeldahl on the whole oxalated plasma without correcting for non-protein nitrogen, fibrinogen was determined by micro-Kjeldahl, and icterus index by comparison of the oxalated plasma with standards prepared according to the method of Farahaugh and Medes.<sup>5</sup>

The animals were maintained on a diet consisting of cane sugar, lard, protein-free butter, bone ash, a salt mixture,<sup>13</sup> cod liver oil, thiamine chloride, and a small amount of protein in the form of a liver extract (Liver extract No. 343\*) or 5 to 20 gm. of fresh pork liver daily. The exact composition of the daily diet of each dog is given in detail in the individual protocols. With one exception the dogs were fasted 24 hours before the administration of chloroform. By fasting we mean a discontinuance of food but a liberal supply of water.

\* We are indebted to Eli Lilly and Company for a supply of this material.

Anesthesia was induced with ether and then chloroform was given by the drop method. A light surgical anesthesia was maintained. All dogs recovered from the anesthesia quite rapidly and were conscious within 2 to 4 minutes.

**Experimental Observations.** We believe the tables given below present adequate evidence to establish our thesis that the liver becomes more susceptible to chloroform injury as the protein reserves are depleted. It is generally accepted that the liver is an important organ for the storage of body protein, but other tissues, for example muscle, are probably actively concerned.

Table 1 is a summary table including 6 fatal cases subjected to brief chloroform anesthesia. Plasma protein levels were not very low except in Experiments 2 and 6, but the protein reserve stores were probably low in all 6. Depletion is readily effected by diet or bleeding. In the fatal cases there was a conspicuous drop in blood fibrinogen within 24 hours after the chloroform anesthesia and a sharp rise in the icterus index. At autopsy, the fibrinogen was very low as evidenced by complete lack of blood clots.

Glycine in considerable amounts given in the diet did not protect the dog (Exp. 5, Table 1) nor did xanthine (Exp. 6) given according to the technique used by Neale and Winter.<sup>11</sup>

TABLE 1.—FATAL LIVER INJURY BY CHLOROFORM ANESTHESIA IN PROTEIN-DEPLETED DOGS.

Experiment No.	Dog No.	Protein depletion.		Plasma protein level, gm. %.	Duration of anesthesia, min.	Hours between anesthesia and death.	Fibrinogen* 24 hrs. after chloroform, mg. %.	Extent of liver necrosis estimated, %.
		Method.	Duration, wks.					
1	38-30	Bleeding + Diet	7	4.28	45	15±	...	90
2	38-18	Diet	4	3.56	30	56	129	60
3	38-144	Bleeding + Diet	6	4.25	20	60	30	50
4	38-196	Bleeding + Diet	6	4.60	15	31	88	75
5	38-274†	Diet	7	5.15	20	15±	...	95
6	38-81‡	Plasma-pheresis + Diet	7	3.85	20	65±	89	70
7	38-241	Diet	9	4.70	20	...§	590	trac ?

\* Blood clots absent at autopsy in each fatal experiment.

† Glycine fails to protect against chloroform liver injury.

‡ Xanthine fails to protect against chloroform liver injury.

§ Single meat feeding gives protection against chloroform liver injury.

A *single protein feeding* in Experiment 7 did prevent completely any liver injury due to 20-minute chloroform anesthesia. Experiment 9 in Table 3 gives support to this important Experiment 7.

More experiments bearing on this point are in progress but these results are so unequivocal as to give some assurance that these single experiments are really significant.

It is of interest to note that the dogs used in these experiments had reserve protein stores of different amounts or conserved these stores over different periods. Dog 38-18 required only 4 weeks of low protein diet, whereas Dog 38-30, with the extra drain of bleeding, required 7 weeks of low protein diet to effect depletion.

The fact that Dogs 38-30, 38-144, and 38-186 were moderately anemic as well as hypoproteinemic at the time of chloroform anesthesia does not appear to have rendered them any more susceptible than the others. It will be recalled that Daft, Robscheit-Robbins and Whipple<sup>1</sup> did not find anemic dogs any more susceptible to chloroform poisoning than normal dogs.

EXPERIMENT 1 (Table 1), Dog 38-30, adult female airedale mongrel.

- Oct 4. Initial plasma protein level, 6.88 gm.%. Weight, 16 kg. Started bleeding and low protein diet (sucrose, 138 gm.; lard, 30 gm.; butter, 14 gm.; bone ash, 4 gm.; salt mixture, 2.5 gm.; cod liver oil, 15 gm.; thiamine, 60 I. U.; liver extract, 2.6 gm.) fed daily in afternoon.
- Oct. 5. Bleeding and diet continued until start of metabolism study. Plasma protein, 4.54 gm.%. Red cell hematocrit, 31%. Weight, 12.7 kg.
- Nov. 26. Plasma protein, 4.16 gm.%. Diet, 30% consumed.
- Nov. 27. Diet, 20% consumed.
- Nov. 28. Fasted.
- Nov. 29. *Chloroform anesthesia 45 minutes*. Recovery uneventful. Refused food offered.
- Nov. 30. Dog found dead in morning. Autopsy showed central areas of lobules deep red, portal areas yellowish. Microscopically there was almost complete disappearance of normal liver tissue with about 90% central hyaline necrosis.

EXPERIMENT 2 (Table 1), Dog 38-18, adult female hound mongrel.

- Oct. 4. Initial plasma protein level, 6.62 gm.%. Red cell hematocrit, 47%. Weight, 12.5 kg. Low protein diet daily (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 15 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.).
- Oct. 31. Plasma protein level, 4.46%. Red cell hematocrit, 42%. Weight, 12.1 kg.
- Dec. 2. Since appetite past several days was poor, diet was supplemented hereafter with 15 gm. fresh pork liver. Weight, 11 kg.
- Dec. 3, 4. Consumed 60% diet.
- Dec. 5. Fasted.
- Dec. 6. Plasma protein level, 3.70 gm.%. Red cell hematocrit, 40%. *Chloroform anesthesia 15 minutes*. Recovery rapid. Somewhat intoxicated. Refused food. Only slight rise in total urinary nitrogen and fourfold increase in uric acid, but no icterus and only slight drop in blood fibrinogen. Consumed average of 40% diet on Dec. 7 and 8.
- Dec. 9. Fasted.
- Dec. 10. *Chloroform anesthesia 30 minutes*. Dog recovered rapidly but later vomited mucus and looked ill.
- Dec. 11. Icterus prominent. Fibrinogen, 129 mg.%. Refused food. Clinically intoxicated. Sugar by vein several times (total sugar 50 gm.) and 200 cc. of 5% glucose subcutaneously.



Dec. 12. Icterus very marked. Fibrinogen 80 mg.%. Despite glucose and transfusions dog died. Total urinary nitrogen for Dec. 10 and 11 almost double the control value of 1.2 gm. per 48-hour period. Slight increase in creatine. About sevenfold increase in uric acid. On autopsy grossly, liver appeared to show severe injury. Microscopically, about 60% of each lobule showed the characteristic hyaline necrosis. Many cells appeared stuffed with glycogen.

EXPERIMENT 3 (Table 1), Dog 38-144, adult female hound mongrel.

- Jan. 12. Plasma protein level, 6.53 gm.%. Red cell hematocrit, 45%. Started low protein diet and bleeding (sugar, 128 gm.; lard, 27.6 gm.; butter, 13 gm.; bone ash, 3.3 gm.; salt mixture, 2.3 gm.; cod liver oil, 5 gm.; liver extract, 2.4 gm.; thiamine, 60 I.U.). Weight, 12.9 kg.
- Jan. 13 to 29. Ate 80 to 90% diet.
- Jan. 30. Plasma protein level, 4.58 gm.%. Weight, 11.8 kg.
- Feb. 1 to 14. Ate 80 to 90% diet. Weight, 12 kg.
- Feb. 15. Fasted.
- Feb. 16. Plasma protein level, 4.25 gm.%. Red cell hematocrit, 30%. Fibrinogen, 277 mg.%. *Chloroform anesthesia 20 minutes*. Recovery rapid. Refuses food.
- Feb. 17. Icterus pronounced. Fibrinogen 30 mg.%. Very ill. Gave several doses intravenous glucose (total sugar 100 gm.).
- Feb. 18. Dog semi-comatose. Despite intravenous glucose and plasma protein dog died. Changes in urinary nitrogen for Feb. 16 and 17 practically same as in Dog 38-18. Autopsy revealed liver lobules which had uniformly deep red central areas, yellowish portal areas. Microscopically, there was at least 50% central necrosis of lobules. Remaining liver cells showed extensive fatty degeneration.

EXPERIMENT 4 (Table 1), Dog 38-186, adult female hound mongrel.

- Feb. 14. Plasma protein level, 6.20 gm.%. Red cell hematocrit, 43%. Bled only twice (total 190 cc.). Started low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 5 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.). Weight, 11.2 kg.
- Feb. 15 to 26. Ate 100% diet.
- Feb. 27 and 28. Ate 75% diet.
- Mar. 1 and 2. Ate 50% diet. Weight, 9.8 kg.
- Mar. 3 to 17. Supplemented diet with 5 gm. fresh liver daily. Ate 100%.
- Mar. 18 to 21. Ate about 50% diet. Increased liver to 10 gm. daily.
- Mar. 22 to 25. Ate 100% diet. Plasma protein level (Mar. 23), 4.70 gm.%. Mar. 26 to 28. Ate only 50% diet.
- Mar. 29. Fasted.
- Mar. 30. Plasma protein level, 4.60 gm.%. Red cell hematocrit, 30%. *Chloroform anesthesia 15 minutes*. Recovery rapid. Refused food.
- Mar. 31. Very sick. Vomited bile-stained mucus several times. Icterus marked. Despite intravenous glucose (40 gm. sugar) and transfusion, dog died. Only slight increase in total urinary nitrogen during 24 hours following anesthesia. Autopsy showed liver lobules standing out uniformly with red central areas and grayish-yellow peripheral areas. Microscopically, the lobules showed about 75% central necrosis. Remaining cells showed extensive fatty degeneration.

EXPERIMENT 5 (Table 1), Dog 38-274, adult female hound mongrel.

- Mar. 30. Weight, 9.5 kg. Placed on low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; cod liver oil, 5 gm.; fresh pork liver, 5 gm.; thiamine, 60 I.U.).
- Apr. 1 to May 15. Average 95% food eaten. Plasma protein level (May 15), 4.50 gm.%. Red cell hematocrit, 47%.

- May 16 and 17. Added 23 gm. glycine to regular diet. Ate 60%.
- May 18. Added 23 gm. glycine to regular diet. Ate 90%. Weight, 8.4 kg.
- May 19. Fasted.
- May 20. Gave 23 gm. glycine in water by stomach tube 2 hours before start of 20 minutes of chloroform anesthesia. (Plasma protein before anesthesia 5.1 gm.%, red cell hematocrit, 47%.) Recovery rapid. Somewhat intoxicated. Refused food.
- May 21. Dog found dead in morning. On autopsy grossly liver lobules were uniformly red in central areas, and grayish-yellow in peripheral areas. Microscopically, about 95% of liver lobule showed central hyaline necrosis.

EXPERIMENT 6 (Table 1), Dog 38-81, adult female terrier mongrel.

- May 2. This dog was apparently fully recovered from a previous injury produced by 12 minutes of chloroform anesthesia 2 weeks before (described in detail in Exp. 8). Diet same as in Experiment 8 except that vitamins A and D were supplied in the form of navitol. Diet 100% consumed for next 2 weeks. Weight, 6.6 kg.
- May 16 and 17. Plasma protein level, 4.08 gm.%. Ate 100% diet.
- May 18. Weight, 6.2 kg. Finely powdered xanthine (3.5 gm.) was suspended in 40 cc. normal saline, the mixture boiled for 6 minutes, cooled, and injected subcutaneously on left side. Dog appeared somewhat ill but ate 90% diet.
- May 19. Repeated on right side injection of 3.5 gm. xanthine. Dog seems disturbed. Some local heat and tenderness at site of injection of May 18. Fasted.
- May 20. Plasma protein level, 3.85 gm.%. Red cell hematocrit, 37%. Fibrinogen, 390 mg.%. Chloroform anesthesia 20 minutes. Recovery rapid, but dog clinically ill. Local reaction at site of both xanthine injections. Ate 10% diet offered.
- May 21. Very ill. Refused food. Fibrinogen, 89 mg.%. Icterus prominent. Intravenous glucose (sugar 25 gm.). Some vomiting during day.
- May 22. Very ill. Refused food. Fibrinogen, 59 mg.%. Icterus prominent. Vomits frequently. Intravenous glucose (50 gm.). Semi-comatose late in day.
- May 23. Found dead in morning. On autopsy practically all liver lobules had deep red central areas with yellowish peripheries. Microscopically, there was about 70% central necrosis; intact liver cells showed extensive fatty degeneration.

EXPERIMENT 7 (Table 1), Dog 38-241, adult female hound mongrel.

- Apr. 22. Weight, 12.2 kg. Placed on low protein diet (same as diet of Dog 38-274, Exp. 5, Table 1).
- Apr. 23 to 29. Fasted.
- Apr. 30 to June 2. Ate an average of 95% daily diet. May 15 plasma protein level, 4.85 gm.%; red cell hematocrit, 47%; weight, 11.8 kg.
- June 3. Plasma protein level, 4.85 mg.%. Red cell hematocrit, 42%.
- June 4 to 11. Ate an average of 50% of daily diet.
- June 12. Supplemented daily diet with an additional 15 gm. fresh pork liver daily (total 20 gm. daily).
- June 13. Ate 60% diet.
- June 14 to 25. Ate an average of 90% daily diet.
- June 26. Plasma protein level, 4.70 gm.%. Red cell hematocrit, 54%. Ate 75% diet. Weight, 11.4 kg.
- June 27 and 28. Ate an average of 40% diet.
- June 29. Replaced daily diet with single feeding of 630 gm. of lean hamburger steak which was promptly consumed.
- June 30. Fasted.

- July 1. Plasma protein level had risen to 5.80 gm.%. Fibrinogen, 570 mg.%. Red cell hematocrit, 42%. *Chloroform anesthesia 20 minutes.* Recovery rapid and uneventful. Ate 70% of low protein diet offered.
- July 2. Dog in very good condition. No sign of intoxication. Plasma protein level, 5.50 gm.%. Fibrinogen, 550 mg.%. Absolutely no icterus. Ate 95% of low protein diet.
- July 3. Fibrinogen, 440 mg.%. Very faint trace of icterus in plasma. Blood formed firm clot readily. Ate 80% diet.
- July 4. Fibrinogen, 370 mg.%. Dog in excellent condition. Very faint trace of icterus in plasma. Returned to kennels. Weight, 11.4 kg.

Experiment 7, Table 1, which shows a striking protection against chloroform poisoning due to a single large protein feeding is of such significance that it must be repeated many times. It will be worth while to test the effectiveness of a large injection of plasma protein a few hours before chloroform anesthesia in the protein depleted dog. Experiment 9, Table 3 (Dog 37-177), given below is in complete harmony with Experiment 7, and gives strong support to the observation that protein administration (liver feeding) protects and protein withdrawal in the same dog renders the dog susceptible to chloroform poisoning.

As several of the above experiments (Table 1) showed that 20 minutes of chloroform anesthesia was almost invariably fatal and that even 15 minutes might be fatal, it was decided to try 12 minutes to obtain a severe but non-fatal chloroform injury so that nitrogen partition in the urine might be studied.

TABLE 2.—PROTEIN DEPLETION (PLASMAPHERESIS AND DIET) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Experiment 8—Dog 38-81

No.	Period.		Total nitrogen, mg.	Urea + NH <sub>3</sub> nitrogen.		Uric acid nitrogen, mg.	Fibrinogen,* mg. %.	Icterus index.	Plasma protein level, gm. %.
	Length, hrs.			Mg.	%.				
1	48		1410	705	50	11.1			
2	48		1130	670	59	8.0	230	0	4.11
<i>Chloroform Anesthesia—12 Minutes.</i>									
3	24		1070	790	74	10.7	79	10	4.35
4	24		970	690	72	14.4	116	12	4.42
5	48		1280	810	63	29.7	157	5	3.85
6	48		770	340	45	24.6			
7	48		740	370	49	19.6			
8	48		900	490	55	17.5	210	tr.	4.08
9	48		740	420	56	9.7			

\* Fibrinogen and plasma protein figures in this table and Tables 3 and 4 were obtained from blood samples taken at the close of periods indicated.

Table 2 presents data obtained from Dog 38-81, Experiment 8. Following chloroform anesthesia, the rate of urinary nitrogen excretion was nearly double that of the control period, but approached normal within 48 hours in Period 5. The percentage of urea and ammonia nitrogen, which was low in the control periods rose markedly to 74% in the 48 hours after anesthesia, dropped to a low of 45% in Period 6, then rose to control values in Periods 8 and 9. In other

words, the *conservation* of the materials which contribute to the formation of urea and ammonia already conspicuous in the control periods becomes accentuated in Periods 6 and 7.

Figures for *creatinine* and *creatinine* are not shown in the table because no significant changes were observed. This is in striking contrast to the large increase in creatine seen in the normal<sup>8</sup> or anemic<sup>1</sup> dog after severe liver injury by chloroform.

The rate of uric acid excretion rose to three times control values in Periods 3 to 5, and returned slowly to normal in Period 9.

The drop in fibrinogen and rise in the icterus index indicate a definite liver injury with central hyaline necrosis.

CLINICAL EXPERIMENTAL HISTORY DURING METABOLISM STUDY PERIOD  
(Table 2). Dog 38-81, adult female terrier mongrel.

- Apr. 7. Plasma protein level, 4.96 gm.%. This dog had been subjected to plasmapheresis for 3½ weeks on a diet similar to that of Dog 37-177 (Exp. 9). Until Apr. 13 ate completely a daily diet of 80 gm. sucrose, 8 gm. filtered butter; 3 gm. salt mixture; 5 gm. cod liver oil; 60 I.U. thiamine; 5 gm. fresh pig liver. Weight, 7.1 kg.
- Apr. 13. To remove fats, diet changed to 100 gm. sucrose; 3 gm. salt mixture; 3 gm. bone ash; 40 I.U. thiamine; 7 drops Navitol; 5 gm. fresh liver. Completely eaten on each of following days (Apr. 20 excepted).
- Apr. 17. Catheterized and bladder rinsed to start urine collections. Given 200 cc. water daily by stomach tube.
- Apr. 20. Dog fasted. Weight, 6.8 kg.
- Apr. 21. *Chloroform anesthesia 12 minutes*. Recovery rapid. Ate 100% diet.
- Apr. 22. Obviously intoxicated, seems ill. Ate 10% diet.
- Apr. 23. Considerably brighter. Ate 90% diet.
- Apr. 24 to May 3. Dog in good condition. Weight, 6.5 kg.

Experiment 9, Dog 37-177 (Table 3), differs from those on the other dogs in that the dog was on a *diet containing adequate protein* in the form of 40 gm. of fresh pork liver daily, but the animal's *protein reserves* were kept in a depleted state by the drain of daily plasmapheresis. Twelve days prior to the anesthesia described in this experiment, the dog was given 20 minutes of chloroform anesthesia and showed practically no sign of injury but on no day was the dog deprived of the liver-containing diet. In Experiment 9 the dog was *fasted 24 hours* before, and 48 hours after, chloroform anesthesia, and the blood and urinary findings indicate that at least a moderate liver injury was produced. The absence of the liver diet to compensate for the protein depletion by plasmapheresis here seems to be the factor favoring liver injury. The changes in urinary nitrogen, fibrinogen, and icterus observed here are qualitatively much the same as those seen in Table 2, Dog 38-81. The comparatively high control urea-ammonia nitrogen per cent seen in the preliminary periods is followed by a slight rise in the 48 hours after the chloroform (Periods 3 and 4), and by a significant fall in Periods 5 and 6 ("reaction of conservation") with a return to normal in Periods 7 and 8. The comparatively high control urea-ammonia nitrogen

per cent is to be attributed directly, no doubt, to the higher protein intake. Creatine and creatinine values showed no significant changes and are not here recorded.

TABLE 3.—PROTEIN DEPLETION (PLASMAPHERESIS) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Experiment 9—Dog 37-177

No.	Period.		Total nitrogen, mg.	Urea + NH <sub>3</sub> nitrogen.		Uric acid nitrogen, mg.	Fibrinogen, mg. %.	Icterus index.	Plasma protein level, gm. %.
	Length, hrs.			Mg.	%.				
1	48		2200	1660	75.4	11.9			
2	24		1260	950	75.4	4.3	490	0	3.81
<i>Chloroform Anesthesia—20 Minutes.</i>									
3	24		1330	1030	77.5	6.4	310	14	3.93
4	24		2050	1610	78.5	9.0	56	8	3.75
5	24		1190	830	69.9	16.6	140	9	3.72
6	48		1560	1020	65.7	20.2	264	1 ±	4.36
7	48		1920	1460	76.2	25.5	303	1 ±	4.44
8	48		2310	1740	75.2	26.8			

CLINICAL EXPERIMENTAL HISTORY DURING METABOLISM STUDY PERIOD  
(Table 3).

Dog 37-177, female adult poodle terrier mongrel, was depleted by daily plasmapheresis and for 4 weeks before metabolism period, plasma protein level was below 4.6 gm. %. Diet daily consisted of 40 gm. fresh pork liver, 75 gm. cane sugar, 5 gm. cod liver oil, 13 gm. lard, 5 gm. bone ash, 1 gm. salt mixture.

Dec. 25. Started urine collection. Ate 96% diet. Weight, 6.1 kg.

Dec. 26. Ate 60% diet. Plasma protein level, 4.27 gm. %.

Dec. 27. Fasted.

Dec. 28. *Chloroform anesthesia 20 minutes.* No diet offered. Dog somewhat intoxicated and looks ill, but fairly active.

Dec. 29. Dog obviously ill, although fairly active. Fasted.

Dec. 30. Dog fairly active. Ate 90% diet.

Dec. 31 to Jan. 4. Dog ate average of 90% diet. Very active. Appears normal. Weight, 5.7 kg.

Table 4 summarizes data from Experiments 10 and 11 on the same dog (37-233). Experiment 10 shows the effect of 15 minutes of chloroform and Experiment 11 the effect of 12 minutes of chloroform anesthesia. The results of both experiments are essentially the same and are very similar to those obtained in Experiment 8. In Experiment 10 the total urinary nitrogen excreted in the 48 hours after anesthesia (Periods 3 and 4) was nearly twice that of the control periods, but this is a small absolute increase in total nitrogen. In Periods 5 and 6 the total nitrogen drops toward the initial control values. In the control periods the urea-ammonia nitrogen per cent has the typically low values we have come to associate with the protein-sparing action of a diet high in carbohydrate and fat and very low in protein. The liver injury results in a marked rise of the urea ammonia fraction (Periods 3 and 4) which then falls off to values even lower than those of the control periods. This perhaps

indicates an extremely efficient reaction of conservation on the part of an animal that has comparatively little protein to use for repairing the liver injury plus replacement of general protein wear and tear. The uric acid excretion shows an immediate increase after anesthesia, rising to a maximum in Period 3 and dropping off only very slowly (Exp. 10). Blood fibrinogen falls and the icterus index rises due to the liver injury and the changes are obvious in the 4 days following the chloroform anesthesia. Creatine and creatinine show insignificant changes from day to day and are not included in the table.

TABLE 4.—PROTEIN DEPLETION (BLEEDING AND DIET) INCREASES SUSCEPTIBILITY TO CHLOROFORM POISONING AND LIVER INJURY.

Experiment 10—Dog 37-233

Experiment 15—Dog 57-255								
Period.		Total nitrogen, mg.	Urea + NH <sub>3</sub> nitrogen.		Uric acid nitrogen, mg.	Fibrinogen, mg. %.	Icterus index.	Plasma protein level, gm. %.
No.	Length, hrs.		Mg.	%.				
1	48	1120	625	56	6.9	..	0	
2	48	1050	595	57	6.4	386	0	5.18
<i>Chloroform Anesthesia—15 Minutes.</i>								
3	24	1020	722	71	9.2	292	17	5.00
4	24	1050	748	71	10.4	194	15	4.99
5	24	796	506	64	12.2	135	15	4.65
6	24	592	309	52	10.1			
7	48	940	445	47	20.8	253	1+	5.22
8	48	891	392	44	18.0			
9	48	842	418	50	18.0			

Experiment 11—Dog 37-233

1	48	846	464	55	6.2	346	0	5.15
<i>Chloroform Anesthesia—12 Minutes.</i>								
2	24	1030	786	76	22.4	166	17	4.60
3	24	983	703	72	35.5	78	16	4.82
4	48	1080	618	57	61.7	131*	15*	4.60*
5	48	885	413	46	60.1			
6	48	832	381	46	62.2	195	1+	

\* Average of figures for two 24-hour samples.

CLINICAL EXPERIMENTAL HISTORY DURING EXPERIMENTS 10 AND 11.

EXPERIMENT 10, Dog 37-233, Boston bull female.

- Dec. 28. Plasma protein level, 6.41 gm.%. Red cell hematocrit, 53%. Started bleeding and low protein diet (sugar, 118 gm.; lard, 25.5 gm.; butter, 12 gm.; bone ash, 3.1 gm.; salt mixture, 2.1 gm.; liver extract, 2.2 gm.; thiamine, 60 I.U.). Weight, 11.6 kg. Bleeding at intervals continued to Feb. 4. Ate average of 65% diet in this period.
- Jan. 30. Gave 64 mg. colloidal iron\* by vein because of low hematocrit.
- Feb. 11. Gave another 64 mg. colloidal iron by vein.
- Feb. 23. Supplemented diet with 5 gm. liver daily.
- Feb. 25. Started urine collection and metabolism study. Ate 50% diet.
- Feb. 26. Ate 50% diet.
- Feb. 27 and 28. Fasted.
- Mar. 1. Weight, 9.1 kg. *Chloroform anesthesia 15 minutes.* Recovery rapid. Ate 80% diet offered.

\* We are indebted to Dr. David Loeser of Loeser Laboratory Inc. for a supply of this material.

- Mar. 2. Somewhat ill. Refused food.  
Mar. 3. More active but refused food.  
Mar. 4. Ate 10% diet.  
Mar. 5. Ate 100% diet.  
Mar. 6 and 7. Ate average of 50% diet.  
Mar. 8 to 11. Ate average of 60% diet. Weight, 8.7 kg. Dog in good condition at end of experiment.

EXPERIMENT 11, Dog 37-233.

- Mar. 15. Weight, 9.7 kg. Diet changed by removing liver extract and adding 20 gm. fresh pork liver daily. Ate 90% diet.  
Mar. 16 to 31. Ate average 60% diet.  
Apr. 1. Started urine collection and metabolism study.  
Apr. 2. Fasted.  
Apr. 3. *Chloroform anesthesia 12 minutes*. Recovery rapid. Ate 40% diet.  
Apr. 4 and 5. Somewhat intoxicated and ill. Ate average 55% diet.  
Apr. 6. Ate 15% diet.  
Apr. 7 to 13. Ate average 50% diet. Dog returned to kennel in good condition, weighing 7.8 kg.

**Discussion.** The following paper by Messinger and Hawkins gives experimental data indicating the importance of diet during administration of arsenicals and their experiments are in harmony with the chloroform experiments recorded above. Practically all workers in this field agree that sugar and proteins have some protective action, that fat gives no protection and may actually predispose to liver injury. The older literature and theories were reviewed some years ago by Davis and Whipple.<sup>3</sup> Recent experiments by Goldschmidt, Vars and Ravdin<sup>6</sup> show that mice are protected by protein diets against chloroform anesthesia. They state<sup>12</sup> that sodium ricinoleate and xanthine protect against chloroform poisoning and believe the reaction to be non-specific.

It is well to admit first as last that we do not have any satisfactory hypothesis to explain the toxic action of chloroform upon liver cells. Of all the many proposals none gives the slightest comfort to those who would understand why the liver cells are picked out in preference to other active cells rich in ferments, for example, pancreas and kidney. Some authors<sup>7,10</sup> ascribe the chloroform injury to phosgene or hydrochloric acid liberated by the cellular oxidation of chloroform. Davis<sup>2</sup> has reported experiments which rather effectively dispose of the thesis that chloroform liver injury is due to disturbance of cell oxidation. The failure of large glycine feedings to prevent serious liver injury from 20 minutes chloroform anesthesia (Exp. 5, Table 1) may be used in the argument that the deamination of glycine in the liver (with ammonia liberated) does not protect against chloroform liver injury as explained on the theory of free hydrochloric acid derived from the chloroform by cellular oxidation. Whatever explanation is preferred, glycine does not protect.

There is pretty general agreement that carbohydrate does give some protection against chloroform liver injury.<sup>4</sup> In view of the great importance of the cell protein stores, it may be argued that

the efficacy of the carbohydrate diet is due to "protein-sparing at the source" and therefore is not primary but secondary.

Clinically and anatomically the *protein depleted* dog shows signs of severe liver injury (Exps. 8, 9, 10, 11) but the increase in total urinary nitrogen is small compared with that recorded for the *non-depleted* dog with a severe liver injury.<sup>1,4</sup> We may choose to explain this observation as due to a diminished store of body protein vulnerable to insult by toxic split products derived from the dead and autolyzing liver cells, or to a very efficient reaction of nitrogen conservation, or both. The very low figures for percentage of urea and ammonia in the urine indicate that the conservation of nitrogenous material becomes accentuated when the liver injury is being repaired.

No significant changes in creatine excretion following liver injury in the protein depleted dog are recorded. This is in conspicuous contrast to the large increases in creatine excretion observed in the normal or anemic non-depleted dog due to chloroform liver injury.<sup>1</sup> Assuming that practically all creatine is found in the muscles we may relate this difference to the presence of protein stores in the muscles which are injured and as a result creatine is set free. The alternative is to us less probable—that all creatine set free is recaptured or used in the emergency due to protein depletion and protein deficiency.

The large increase in uric acid excretion following chloroform in the depleted dog is comparable to that seen in the normal dog;<sup>14</sup> this along with the pronounced fall in blood fibrinogen is evidence that the liver injury produced by the short period of anesthesia in the depleted dog is fully as severe as that produced by the longer period of anesthesia in the normal dog. The fact that the enhanced uric acid excretion continues over a much longer period in the depleted dog than in the normal dog is perhaps referable to the slower repair of injured liver tissue in the former.

**Summary.** Liver injury due to chloroform anesthesia increases in extent as the protein body stores are depleted. In a protein-depleted dog 15 to 20 minutes of chloroform anesthesia is frequently fatal with extensive hyaline liver necrosis and the typical picture of chloroform poisoning. Twelve minutes of chloroform anesthesia in a protein-depleted dog will cause moderately severe liver injury. Protein depletion is effected by low protein diets alone or combined with bleeding or plasmapheresis.

Control experiments in dogs without protein depletion indicate that 90 minutes of chloroform anesthesia can be tolerated with but little liver injury.

In the depleted dog xanthine subcutaneously or glycine by mouth do not protect, but a single large protein feeding 36 hours before chloroform anesthesia may protect against liver injury.

In contrast to the non-depleted or anemic dog the urinary creatine does not increase after liver injury in these protein-depleted dogs.



The protein-depleted dog compared with the non-depleted dog after chloroform liver injury shows relatively little increase in total urinary nitrogen.

There is a conspicuous increase in uric acid excretion in these depleted dogs after chloroform liver injury, perhaps due in part to liver function impairment and disturbance of its normal capacity to convert uric acid to allantoin.

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### ARSPHENAMINE LIVER INJURY MODIFIED BY DIET. PROTEIN AND CARBOHYDRATE PROTECTIVE, BUT FAT INJURIOUS.

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SINCE the arsenical compounds have proved so effective in the antisyphilitic treatment, countless numbers of patients receive such drugs for extended periods. One of the not too uncommon complications arising from the use of arsenicals is injury of the liver of varying degrees of severity. The problem as to how to prevent and treat such injuries continuously confronts the clinician. Since Davis and Whipple<sup>2</sup> demonstrated that carbohydrates protected the liver against chloroform injury and also aided in its regeneration, it has been customary practice to administer carbohydrates in liberal amounts in any type of liver injury.

In 1931 Craven<sup>1</sup> reported that he found a high fat diet most efficacious in preventing "acute yellow atrophy" of the liver of dogs, due to arspenamine. Both protein and carbohydrate diets were reported as inferior. He based his findings on the histologic changes present in the livers. Schiffrin<sup>4</sup> stated that contrary to Craven's report he found a protein diet was more satisfactory than

fat in minimizing arspfenamine injury and that from histologic study regeneration was more rapid and complete with the meat diet.

Obviously the question of arspfenamine liver injury which is of acute interest to the clinician is open for discussion, with conflicting claims coming from relatively similar experiments.

In our experiments we have used comparable types of diet and the evidence is clear-cut that the meat diet is very effective in protecting the liver against arspfenamine injury. Carbohydrate is of distinct protective value. Fat diets are deleterious, as the injury that follows the injection of arspfenamine may be severe and progressive with death resulting from liver insufficiency.

In confirmation of the value of protein as a protective agent against liver injury are the data reported by Miller and Whipple in an accompanying paper. They have demonstrated that when the protein stores of a dog are depleted that the liver becomes very sensitive to chloroform and that extensive injury results from only 15 to 20 minutes of light chloroform anesthesia.

**Methods.** The dogs used were all healthy young mongrel adults weighing from 10 to 17 kg. In each experiment there was as a rule 1 dog on each type of diet and the arspfenamine was given according to weight. The initial dose was 0.03 gm. per kg., with increase from week to week as indicated in the tables. A standard brand of arspfenamine was used and the same lot of drug was given throughout an experiment so that any possible variations in toxicity of different samples are ruled out. The drug was injected by means of a gravity burette into the external jugular veins.

The carbohydrate diet consisted of steamed rice, cane sugar, 20 gm.; dextrose, 15 gm.; Wesson salts, 4 gm.; cod-liver oil, 5 cc.; thiamine chloride, 33 units; Klim, 10 gm. (a whole milk powder), with water added to make it into a semifluid mass. From 600 to 800 gm. of this mixture was fed daily and the dogs maintained their weight. By macro-Kjeldahl analysis this diet contained an average maximum protein value of 3.5%.

The fat diet was composed of lard, 70 gm.; protein-free butter fat, 50 gm.; cod-liver oil, 50 cc.; kaolin, 2 gm.; bone ash, 4 gm.; Wesson salts,<sup>5</sup> 4 gm.; and thiamine chloride, 33 units. The dogs ate the diet satisfactorily and were maintained in good clinical condition.

The protein diet consisted of 1 pound of hamburg with low-fat content.

The icteric index was estimated directly on plasma obtained from centrifugalized oxalated blood samples in hematocrit tubes, comparing with color standards according to the method of Farahaugh and Medes.<sup>3</sup>

**Experimental Observations.** Since all the experiments were carried out under standard conditions we have listed the dogs in tables according to the diet fed, rather than discussing each of the experiments separately. Such grouping of the dogs allows for more brevity and also for more clarity of exposition and brings out contrasts between the three groups.

All of the dogs (Table 1) except 38-169 were fed their protein diet for 1 week before the initial injection of arspfenamine. Dog. 38-169 for a month preceding the meat diet received kennel diet plus  $\frac{1}{2}$  pound of salmon so as to be certain its protein stores would be replete. Under the heading icteric index the "0" day represents

the day of injection and the control level of the icteric index found in the sample of blood withdrawn just prior to the injection of the drug.

TABLE I.—PROTEIN DIET.

Dog.	Arsphenamine, gm./kilo.	Icteric index.								Biopsy liver injury.
		Days after injection.								
		0	1	2	3	4	5	6	7	
38-53 . . . . .	0.030	0	2	1						Slight
	0.035	0	5	3						
	0.040	2	3	2						
38-169 . . . . .	0.035	0	—	0	0					
	0.040	0	0	1	0					
	0.045	0	0	0						
38-19 . . . . .	0.040	0	2	1	1	0				
	0.045	0	0	0						
38-94 . . . . .	0.035	0	3	2						Slight
	0.040	0	0	1						
	0.045	0	1	0	0					
38-62 . . . . .	0.030	0	1	0						Slight
	0.035	0	0	—	0	0				
	0.040	0	—	0	0					
	0.045	—	1	1						
	0.050	1	—	2	2	—	1			

Arsphenamine injected at weekly intervals.

It is apparent that the high-protein diet was most effective in protecting the liver against severe injury, as at no time was there any conspicuous elevation of the icteric index. Histologic examination of the livers showed minimal injury. The dogs continued to eat their full ration and never showed the slightest evidence of clinical intoxication.

Dog 38-53 was killed with ether on the third day after the last injection and autopsied together with the dog on the high-fat diet which became very ill following the third injection of the drug. At autopsy no gross abnormalities were found in Dog 38-53. Histologic sections of the liver showed that cells in the central area had been injured and the cell debris cleared away leaving collapsed stroma. Occasional portal areas showed similar loss of cells but the lesion was mainly central. There were some phagocytic cells containing brown pigment which was apparently lipochrome in character. Special stains revealed no fat and some glycogen was found in liver cells.

Biopsy of the liver of Dog 38-94 showed a minimum amount of injury with loss of a few cells in the central areas. Biopsy was done on the sixth day after the last injection of the drug. In portal areas there were occasionally a few necrotic liver cells surrounded by neutrophils. Some glycogen was present in the liver cells but no fat. Pigmented phagocytic cells were to be seen in the areas that had been injured.

Biopsy from Dog 38-62 on the third day after the last injection showed a similar picture as regards extent of damage. Occasional mitotic figures were present indicating regeneration.

TABLE 2.—CARBOHYDRATE DIET.

Dog.	Arsphenamine, gm./kilo.	Icteric index.								Autopsy liver injury.
		Days after injection.								
		0	1	2	3	4	5	6	7	
38-189 . . . .	0.040	0	0	0	1	0				
	0.045	0	1	0						
	0.050	0	1	2						
38-179 . . . .	0.035	0	—	0	0					
	0.040	—	2	0	0					
	0.045	—	0	0						
38-50 . . . . .	0.030	0	0	0	—	0				
	0.035	0	—	4	1					
	0.040	1	3	2						Slight
38-96 . . . . .	0.035	0	24	38						Lethal
38-63 . . . . .	0.030	0	0	—	0	0				
	0.040	0	—	2	1					
	0.045	1	—	2	1					
	0.050	3	3	7	9					Slight
38-143 . . . . .	0.030	0	8	3	—	5				
	0.035	4	6	—	19	21	12	—	12	
	0.040	0	—	4	4					
	0.045	4	—	7	6					
	0.050	5	—	12	—	15				Moderate

The dogs received the carbohydrate diet for a week previous to the first injection of the drug. Dog 38-179 was fed  $\frac{1}{2}$  pound of salmon on the kennel diet for a month prior to the carbohydrate feeding, so its stores of protein must have been adequate. If we momentarily disregard Dog 38-96 and Dog 38-143, it then appears that on comparable regimens these carbohydrate dogs have an icteric index picture closely simulating that of the protein dogs. The histologic sections, however, reveal that there was a little more injury to the liver and the dogs did show slight intoxication following the injection of the drug, as they left some food for a day or two. Recovery was prompt, however.

Dog 38-96 was apparently very susceptible to the arsphenamine, as the initial dose of 0.035 gm. per kg. caused severe reaction. It showed diarrhea, bouts of vomiting, and on the morning of the third day was found dead. Autopsy revealed generalized jaundice, and petechial hemorrhages were present in the subcutaneous tissues. The liver grossly was light brown in color with numerous pin-point red and yellow areas on the surface. The cut surface was friable, and central areas were red in color and tended to be sunken below the surface. Sections showed extensive hyaline necrosis with neutrophil infiltration with only a few liver cells remaining about the

portal areas and some of them contained fat. No glycogen was found in the persisting liver cells.

Dogs 38-50, 38-63, and 38-143 were killed with ether on the second or fourth day after the last injection and autopsied at the same time as comparable dogs on the fat diet. Grossly, the organs presented a normal appearance.

The sections of liver from Dog 38-50 again showed only slight injury in the central areas with loss of a few liver cells. No areas of hyaline necrosis were found. Pigmented phagocytic cells were present in the injured areas. The liver cells contained a large amount of glycogen and no fat was present. The liver of Dog 38-63 was similar in appearance.

Dog 38-143 showed more injury, as these areas about central and portal areas were larger. No hyaline necrosis was found, but there was loss of liver cells with numerous pigmented phagocytic cells. There was only a moderate amount of glycogen in the liver cells and no fatty degeneration was apparent.

It is apparent that carbohydrate afforded protection but not quite as much as the meat diet.

TABLE 3.—FAT DIET.

Dog.	Arsphenamine, gm./kilo.	Icteric index.								Autopsy liver injury.
		Days after injection.								
		0	1	2	3	4	5	6	7	
38-211 . . . .	0.035	2	—	4	2					
	0.040	2	15	16	35	48				
38-54† . . . .	0.030	0	0	0						Slight
	0.035	0	6	2						
	0.040	2	24	51						
38-158* . . . .	0.040	0	4	3	2	0				Moderate
	0.045	0	19	79	159					
38-52† . . . .	0.035	0	—	—	46	52	45			Lethal
	0.040	39	—							
38-48 . . . .	0.030	0	9	4	6					
	0.035	4	6	6	8	13	7			
	0.040	6	8	6						
	0.045	5	13	13	7	—	—			
	0.050	18	—	83						
38-67 . . . .	0.035	0	6	4	3	2				Severe
	0.040	2	4	4	4					
	0.045	0	10	15	21	35	36			
38-62 . . . .	0.035	0	—	8	18	11	9			Moderate
	0.040	7	10	13	19	10	9			
	0.045	7	—	23						
* 10% protein added to fat diet. † 20% protein added to fat diet. ‡ 30% protein added to fat diet.										

In Table 3 the data obtained from the high-fat diet dogs are tabulated. Dog 38-211 received kennel diet and  $\frac{1}{2}$  pound of salmon for a month prior to receiving the fat diet. All of these dogs showed a drop in total plasma proteins after being on the fat diet from 7 to

10 days. This change was, on the average, a fall from a normal value of 6.4% to a lower value of about 5.5%. The carbohydrate dogs did not show any decrease in their plasma protein levels. This decrease in plasma protein, although slight, may be an indication that protein stores were being drawn upon, since the fat diet would scarcely protect the protein stores as carbohydrate may do.

All of the fat-fed dogs were easily injured by the arsphenamine, as indicated by the icterus that developed. On continued administration of the drug, progressive jaundice developed and intoxication was so marked that death occurred; or they were killed with ether, because it was obvious that death would ensue. The addition of varying amounts of protein to the fat diet of 3 of the dogs had no significant mitigating effect on the toxic reaction.

Dog 38-52 was found dead on the morning after the second injection. Its initial response to the first dose of the drug was severe, as seen in the table, and we were not surprised at the early fatal outcome. The other dogs were killed with ether, except Dog 38-211 which will be discussed under Table 4.

At autopsy, all the fat-fed dogs showed generalized jaundice and some exhibited bleeding tendencies due to lack of fibrinogen, prothrombin, or both. The livers were a light brown-yellow in color and obviously fatty. They tended to be friable and the central portions of the lobules frequently were depressed slightly below the surface. The dogs were killed and autopsied on the second, third, or fifth days after the last injection of arsphenamine.

Dog 38-52 showed very extensive liver injury as at least one-half of each lobule had been destroyed. All liver cells about the central areas were gone and there was hemorrhage and wandering-cell infiltration with considerable brown pigment in the large phagocytic cells. On the periphery there was fatty degeneration, and it was only about portal areas that one found relatively normal-appearing liver cells. With special stains even these latter cells were found to contain fat. No glycogen was present.

Dog 38-54 showed generalized fatty degeneration, but only occasional necrotic liver cells. Bile canaliculi contained brown inspissated bile. No glycogen remained.

Dog 38-48 showed a moderate degree of fatty degeneration with a little glycogen persisting. There was collapse of central areas with loss of liver cells. Some mitotic figures were present and there were many pigmented phagocytic cells. Areas of injury were found about portal regions also.

Dog 36-159 showed marked fatty degeneration with areas where liver cells had been destroyed and one saw only stroma and phagocytic cells. Both central and portal regions were involved. There was some glycogen in better preserved liver cells. Kidney tubules contained bile-stained material and some of the epithelium of collecting tubules contained fat.

Dog 38-67 showed hyaline necrosis of approximately one-quarter

of each lobule and in addition there was evidence of previous loss of cells. Phagocytic cells containing brown pigment were present. The lesion was both central and portal in distribution. Fat was present in many of the remaining liver cells and no glycogen was found.

TABLE 4.—THE EFFECT OF INTERCHANGING DIETS.

Dog.	Diet.	Arsphenamine, gm./kilo.	Icteric index.							
			Days after injection.							
			0	1	2	3	4	5	6	7 8
38-211 . . .	Protein	None	48	—	24					
		0.045	21	20	13	—	—	—	10	
		0.040	5	4	4	3				
		0.045	2	2	2	2	2			
	Fat	None	2	—	—	—	21			
		0.050	21	—	26	—	—			
38-169 . . .	Fat	0.040	0	5	4	4				
		0.045	3	21	28	34	37			
	Protein	None	37	21	—	—	—	—		
		0.050	6	6	5	—	4			
	Fat	None	3	—	5	—	—	27	26	— 11
38-189 . . .	Fat + 20% protein	0.050	0	12	25	—	77			
	Carbohydrate	None	77	63	—	14				
	Fat + 20% protein	None	14	14	12	8				
		0.050	7	—	48	55				
38-179 . . .	Fat	0.040	2	12	10	6				
		0.045	2	4	4	3	2			
		0.050	7	17	33	16				
38-19 . . .	Fat	None	0	—	—	—	4			
		0.050	4	16	16					
	Carbohydrate	None	16	—	—	—	—	—		
		0.050	2	—	4	2				
		0.050	1	—	2	1				

Dog 38-62 previously had been fed protein and a biopsy taken after 5 injections of the arsphenamine showed only minimal injury as described. After it had been on a fat diet and had received 3 doses of arsphenamine, the liver sections showed extensive injury with loss of liver cells in portal or central areas. There was some fatty degeneration, and some necrotic liver cells were to be seen. There were mitotic figures indicating attempted repair. No glycogen was present.

Review of these sections indicates different types and different grades of injury and it is impossible to predict from histologic changes what the icteric index might be or how severe was the state of intoxication.

In Table 4 we have listed a group of animals who have previously appeared in the other tables according to the diet fed them. When Dog 38-211 on the high-fat diet became toxic and inactive with an icteric index of 48, as seen in Table 3, we substituted the protein diet for the high-fat diet in an effort to save this animal. Promptly the icterus level began to fall and the dog became active again.

Despite 3 subsequent arsphenamine injections, the bilirubinemia continued to decrease and the dog appeared well. Once again, as seen in Table 4, the dog was returned to its original high-fat diet, and after 4 days the icteric index had risen from 2 to 21 units simply on change from protein to fat diet without further arsphenamine. We shall again refer to this phenomenon of apparent "delayed jaundice."

Further evidence that Dogs 38-169 and 38-179 were really protected by their respective protein and carbohydrate diets and not refractory to arsphenamine appears when both were placed on fat diets for 1 week and then injected again as indicated in Table 4. Dog 38-169 in particular showed the typical progressive jaundice on the high-fat diet and at the maximum time of injury it had an icteric index of 37, was listless and toxic. We again resorted to the protein diet to save this animal. The icterus soon began to clear and despite another injection of arsphenamine the icterus continued to recede, as the table shows, and the animal remained in such excellent condition that it could be used in the following experiment.

In an effort to reproduce the "delayed jaundice" observed in Dog 38-211, the protein diet of Dog 38-169 was now withdrawn and replaced again by the high-fat diet. As indicated in Table 4, without any further administration of arsphenamine, the dog's plasma bilirubin showed a sharp increase from 3 to 27 units by the fifth day. On the sixth day the icteric index was still 26 and then gradually returned to normal.

The results of feeding the fat diet to protein Dog 38-19 are indicated in Table 4 by the slight but definite "delayed jaundice." The further injurious effect on this dog of another injection of arsphenamine is apparent. Upon again changing this dog's diet from fat to carbohydrate, we see a diminution of the icterus and lack of injurious response despite further arsphenamine administration.

Carbohydrate Dog 38-189 was placed on a fat diet plus 20% protein since little injurious response was obtained on its original carbohydrate diet. After eating the fat diet for a week it was injected as shown in Table 4 and developed the usual severe toxicity and bilirubinemia the dogs on these diets show. The beneficial effect of replacing the fat diet by carbohydrate is further demonstrated. An attempt to reproduce "delayed jaundice" by reversion to the fat diet failed here, but the prompt injurious response of the animal on the fat diet again to arsphenamine was demonstrated, despite the added protein in the fat diet.

**Discussion.** It is of importance to appreciate the fact that even the initial dose of arsphenamine given to these dogs is large. When one considers that an 11-kg. dog receives a minimum of 0.33 gm. of the drug in a single dose, as compared to 0.4 gm. therapeutic dose for a 66-kg. man, it is to be expected that the liver should be injured regardless of the diet fed. Sections of the livers of all the dogs show that some injury has occurred. In the case of the protein-



fed dogs, it is minimal and the liver derangement is so slight that the function of eliminating bile pigments has not been particularly disturbed. In the carbohydrate group the degree of injury as indicated by the icteric index and the histologic changes in the liver varies, but it compares in no way with the extensive damage and dysfunction as exhibited by the fat-fed dogs.

One should note well the fact that dogs that had been protected by meat or carbohydrate diets, when changed over to the fat diet, sustained severe liver injury upon subsequent injection of arsphenamine. This demonstrates that these dogs were not refractory to the drug and also indicates that high-fat diet is injurious, even though the animals' stores of protein may be high.

Conversely, when the fat-fed dogs were severely jaundiced and intoxicated and would not eat well, there was immediate improvement in their condition when the diet was changed to protein or carbohydrate. No further injury occurred to their livers when arsphenamine was subsequently injected.

Further evidence that fat is deleterious is indicated by the data in Table 4. Some of the dogs showed a decided increase in their icteric index when their diets were changed to fat, even though no more arsphenamine was given during the period of fat diet. It is possible that this "delayed jaundice" is caused by fat deposited in the liver which renders the cells susceptible to some arsenic that was present in the body from previous injection. It is not just a flight of fancy to consider that delayed liver injury as displayed by some human beings may be related to their dietary régime.

A high-fat diet may be injurious due to its requirements of sugar for its combustion. This would imply a drain first on the carbohydrate stores and finally on the protein stores. The total plasma protein of the fat-fed dogs showed a slight decrease after 7 to 10 days' feeding and this may be of significance, indicating that the dogs were calling upon their protein stores.

We believe Craven's conclusions are in error mainly because he killed his animals at the first sign of serum jaundice. Deductions drawn from the histopathologic changes in the livers of dogs killed at this stage of the injury could readily lead one to error. It is necessary to follow the animals over considerable periods to observe the icteric index and general clinical developments.

Schifrin<sup>4</sup> disagreed with Craven's conclusions, as he found the protein-fed dogs showed the least injury and that the liver regenerated best on the meat diet.

The value of protein as a protective agent appears to be clearly established, but further studies are required to learn the why of its beneficial effects. It has been customary to give liberal amounts of carbohydrate to patients with liver injury. Some clinicians consider that protein should be restricted in order not to tax the damaged liver. In our experiments, the dogs with severe liver injury showed marked improvement when the fat diet was changed to

protein and there was not the slightest evidence that the meat diet was in any way injurious. We suggest that in the face of liver injury a diet of protein and carbohydrate may prove to be of more value than carbohydrate alone.

**Summary.** When dogs are given arsphenamine in doses of 0.03 gm. per kg. or higher, liver injury results to a greater or lesser degree depending on the diet fed. Protein is found to be most effective in protecting dogs against arsphenamine liver injury. On a protein diet the liver injury is trivial and promptly repaired. A carbohydrate diet also is beneficial, but is not as uniformly protective and the liver injury may be somewhat greater. Fat has proved to be deleterious, as the arsphenamine dogs show marked progressive jaundice, severe liver injury, and may become intoxicated to the point of death.

In certain instances dogs that had been protected by protein or carbohydrate showed a progressive increase in the icteric index when changed over to the fat diet, even though no additional arsphenamine was injected.

When fat-fed dogs that showed severe intoxication due to arsphenamine injury were switched to protein or carbohydrate diets they immediately recovered from the intoxicated state and the icteric index decreased. Subsequent injections of arsphenamine caused no ill-effects as long as the dogs remained on either the protein or carbohydrate diet.

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## USE OF VAPORIZED BRONCHODILATOR SOLUTIONS IN ASTHMA AND EMPHYSEMA.

### A CONTINUOUS INHALATION METHOD FOR SEVERE ASTHMATIC STATES.

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INHALATION of vaporized solutions of bronchodilator drugs by patients with asthma or emphysema has been used for many years. In simplicity of technique, rapidity of action, and in relative freedom

from constitutional side-effects, this method offers practical advantages over the administration of similar drugs by mouth or by hypodermic injection. The extent of distribution and absorption of such solutions, administered by methods of continuous or intermittent inhalation, was studied some years ago by Heubner.<sup>6</sup> Lageder<sup>7</sup> observed increase in vital capacity and velocity of breathing, as well as beneficial clinical results, following continuous inhalation of 1:1000 epinephrin vaporized over 20-minute periods.

The most important advance in practical therapy was made by Graeser and Rowe<sup>4</sup> in 1935, with the introduction of a more concentrated (1:100) solution of epinephrin, used in a hand-bulb atomizer that provided a fine vapor suitable for inhalation. Oral inhalation of vaporized 1:100 epinephrin solution has since been widely used for relief and prevention of asthmatic attacks.

In his most recent paper, Graeser<sup>3</sup> has presented an excellent brief review of earlier work, together with some further observations on the use, by the hand-bulb atomizer, of solutions of epinephrin of various concentrations, and of certain other solutions, notably ephedrin sulphate 10%, and neosynephrin 5%. Graeser concluded that epinephrin 1:100 was, under average conditions, the most practical for the inhalation therapy of bronchial asthma. In some instances, a 1:50 concentration was found to be more effective; in others, 1:200, or lower, was adequate. Inhalation of 10% ephedrine, or of 5% neosynephrin solution, did not give relief. In some instances with children, the use of a mask apparatus, with a motor blower providing a continuous vaporization, was necessary.

It is generally recognized that the hand vaporizer with 1:100 epinephrin solution, has both limitations and disadvantages: 1, It is usually employed for only a few seconds at a time, and the application of the vapor to the bronchial mucous membranes is therefore brief; often insufficient in more severe asthmatic attacks; 2, even the squeezing of the nebulizer and the repeated deep inhalations may be exhausting to a very ill or dyspneic patient; 3, epinephrin 1:100 on prolonged use may be drying and irritating to mucous membranes (Galgiani, Proescher, Dock, and Tainter<sup>2</sup>); 4, this solution, if used intensively or repeatedly over long periods, will in some cases produce undesirable systemic effects, such as headache, palpitation, nervousness, tremor, and so on.

In an attempt to overcome some of these difficulties, we have employed a simple technique for *continuous inhalation* of vaporized bronchodilator solutions. This consists in the use of a pressure tank of oxygen, with the usual reducing valve to regulate flow; attaching the outflow tube to the vaporizer and running in oxygen, at a flow sufficient to produce adequate vaporization. A small motor blower unit can be used instead of a pressure tank; but in our experience, these units usually convey a slight odor to the vapor, which is often disagreeable to the patient.

With a flow of 4 to 7 liters per minute, 1 cc. of solution will be vaporized in from 3 to 10 minutes. The patient simply holds the nozzle of the vaporizer in his oro-pharynx, and breathes quietly; no additional effort is needed.

Two advantages are obtained by this technique: 1, A larger amount of solution is brought into contact with the bronchial mucous membrane than is possible with the use of the hand-bulb, and without effort on the part of the patient. The technique is thus more effective for the very ill bed patient in a severe asthmatic state. 2, Less irritating solutions, with milder bronchodilator action, are often effective in suppressing moderate asthmatic attacks when given by the continuous technique, whereas they are ineffective when used with the hand spray. This is of particular advantage in patients who suffer from dryness and irritation of the air passages after inhalation of vaporized 1:100 epinephrin solution, or when constitutional side-effects occur; especially if such patients have to use the spray frequently during the day, and over prolonged periods of weeks or months.

Neosynephrin hydrochloride is a mild bronchodilator of this type. This substance is chemically closely similar to epinephrin hydrochloride, differing only in having one, instead of two, hydroxyl radicals attached to the benzene ring. It is established as effective in constricting nasal mucous membranes by topical application.<sup>1,5,11</sup> Neosynephrin is said (Fitzhugh<sup>1</sup>) to induce a more lasting vasoconstriction than either ephedrin or epinephrin, when applied locally. After-effects of dryness, irritation, and engorgement apparently do not occur. By subcutaneous injection, this drug has little effect in relieving asthma.

**Procedure.** The technique of continuous vaporization of bronchodilator solutions has been used at the Presbyterian Hospital during the last 18 months, for the treatment of bronchial asthma, and for asthmatic attacks, dyspnea, and cough in patients with pulmonary fibrosis, chronic emphysema and certain cases of bronchopneumonia. Though administered for the most part to bed patients, it has also been tried in ambulatory patients in the Asthma Clinic and the Chronic Chest Disease Clinic.

As stated above, a single treatment consisted in the vaporization, over 3 to 10 minutes' time, of 1 or 2 cc. of bronchodilator solution, the subject holding the nozzle well within his oro-pharynx and breathing quietly throughout the procedure.

As a vaporizer we used the "Vapco" and the "Vaponefrin" models. Both were satisfactory; the Vaponefrin apparatus produced a somewhat more voluminous vapor stream.

**Solutions.\*** In addition to 1 to 100 epinephrin solution, and 1 to 100 neosynephrin solution, we tried mixtures of epinephrin and neosynephrin, and "Vaponefrin" solution, a proprietary product whose composition is stated by the manufacturer to "contain 1 to 100 epinephrin, and 0.5 per cent chlorbutanol."

\* The neosynephrin solution used in this study was supplied through the courtesy of Frederick Stearns & Co.; the Vaponefrin vaporizers and solution through the courtesy of the Vaponefrin Company.

**Results.** In addition to clinical results observed, an attempt was made to obtain an objective measure of change in pulmonary function, in patients who were not seriously ill and who could cooperate in performing respiratory tests. Pulmonary ventilation, vital capacity, and maximum ventilatory capacity were measured in a number of such patients.

There were no consistent changes in resting pulmonary ventilation.

Considerable and significant increase in vital capacity was noted, following continuous inhalation of the spray, in most of the cases of chronic fibrosis and emphysema, and in a number of asthmatic subjects. The results in 26 unselected cases are given in Table 1. This series consisted in 12 ambulatory cases of asthma, studied in the Asthma Clinic, 3 ambulatory cases of chronic emphysema and 9 hospitalized cases of chronic pulmonary disease of various types.

In general, the degree of relief obtained was approximately proportional to the increase in vital capacity.

The ambulatory asthmatic subjects coming in to the Clinic were given the inhalation whether they were having asthmatic symptoms at the time, or not. This probably accounts in part for a large discrepancy in vital capacity change, in individual cases.

In a few instances we have had patients in status asthmaticus who have responded to continuous inhalation spray when other measures have failed. These patients were usually too ill for any respiratory measurements.

Such a case was N. R., a Post Office clerk of 33, who had had bronchial asthma for 4 years. For 2 days prior to his hospital admission, he had been in an almost continuous asthmatic state. This attack had not responded to epinephrin given hypodermically every 2 hours, nor to ephedrin by mouth, about 15 tablets a day. After admission to the hospital, a further injection of epinephrin, and 1 of morphine and atropine, gave no relief. Dyspnea and cough were severe. Half an hour later an inhalation spray, consisting of 7 drops of epinephrin 1 to 100 and 10 of neosynephrin 1%, was given continuously over a 15-minute period. The change in the patient's condition following the inhalation spray was immediate and striking. Pulse dropped from 130 to 100, respirations from 60 to 40, inspiratory stridor disappeared and expiratory stridor was much decreased. Subjectively, dyspnea was relieved. During that night the spray was used 4 times, bringing marked relief on each occasion. No other medication was used except for nasal oxygen, and amytal tablets. During the ensuing 3 days, the spray was used at frequent intervals, for recurring severe asthma. He was much improved. On the fourth day, he was found to respond again to epinephrin hypodermically. Subsequently, the maxillary sinuses were drained, and the asthma gradually subsided.

The subjects with chronic pulmonary disease were having more continuous symptoms, of dyspnea, asthma, and cough, than the ambulatory asthmatic cases, and, as would be expected, their responses to the continuous spray were more uniform.

TABLE 1.—VITAL CAPACITY BEFORE AND AFTER CONTINUOUS INHALATION SPRAY.

Disease.	No. of cases.	Type of treatment.*	Total number of treatments given.	Average vital capacity, cc.		
				Before.	After.	% change.
1. Bronchial asthma .	14	Epinephrin	10	2230	2485	+11.5
		Neosynephrin	18	2090	2340	+11.9
		Vaponefrin	4	1635	2045	+25.1
		Neo.-epi.	2	2350	2410	+2.6
2. Chronic emphysema.	9	Epinephrin	7	1745	1905	+9.2
		Neosynephrin	19	1880	2080	+10.6
		Vaponefrin	2	1525	2000	+31.0
		Neo.-epi.	6	1495	1660	+11.0
		Neo.-vapo.	3	1585	1835	+15.8
3. Tuberculosis and pulmonary fibrosis .	1	Neosynephrin	1	1000	1080	+8.0
4. Ayerza's disease .	1	Epinephrin	1	2100	2340	+11.4
		Neosynephrin	1	1630	2240	+37.4
5. Emphysema and coronary sclerosis .	1	Neosynephrin	1	4790	5100	+6.5

\* Epinephrin = 1:100 epinephrin solution; neosynephrin = 1 to 100 neosynephrin solution; Vaponefrin = Vaponefrin solution; Neo.-epi. = mixture of neosynephrin and epinephrin; Neo.-vapo. = mixture of neosynephrin and Vaponefrin.

In certain instances the change in maximum breathing capacity, that is, the maximum volume of ventilation that the subject could accomplish by voluntary effort,<sup>8</sup> proved a better index of improved pulmonary function than vital capacity. Table 2 gives comparative results in measurement of maximum breathing capacity in 7 cases.

Of the 12 cases of chronic pulmonary disease listed in the tables, all but 2 received appreciable clinical relief from the continuous spray. In 3 instances, the method has since been used successfully by the patients at home for periods of a year or more.

In 1 case, continuous inhalation of neosynephrin vapor brought relief of asthma where epinephrin in any form could not be tolerated. This was B. S. (Table 2), with bullous emphysema and an associated asthmatic dyspnea. Epinephrin hypodermically always produced in this patient severe constitutional symptoms; epinephrin spray caused capillary hemorrhage from the bronchial mucous membranes. After inhalation of 1.5 cc. of neosynephrin a period of asthmatic dyspnea cleared in about 10 to 15 minutes. There was a small increase in vital capacity, and a considerable increase in maximum breathing capacity (Table 2).

Patient G. G. (Table 2) had decided relief from cough following continuous neosynephrin inhalations, though these produced almost no appreciable change either in vital capacity or maximum breathing. This was a woman of 40, with far advanced bilateral tuberculosis and associated pulmonary fibrosis, who was suffering from obstructive dyspnea at rest, which was present constantly, but aggravated by severe spasmodic attacks. The obstructive breathing was both inspiratory and expiratory. Bronchoscopy

showed only marked bronchial spasm, with stiff, contracted bronchi. She had an arterial oxygen saturation of 87%. There was no appreciable change in vital capacity either on continuous spray, or after epinephrin hypodermically. The patient felt subjectively relieved after the spray, however, and was able to raise sputum.

TABLE 2.—MAXIMUM BREATHING CAPACITY BEFORE AND AFTER CONTINUOUS INHALATION SPRAY.

Case.	Diagnosis.	No. obs.	Treatment.	Maximum ventilation, liters/min.		Remarks.
				Before.	After.	
F. H.	Emphysema	1	Neosynephrin, 1 cc.	27.0	37.1	Hypodermic more effective.
		1	Epinephrin, 1 cc.	34.1	45.1	
		1	Epi., hypo., 1 cc.	31.2	48.4	
H. T.	Emphysema	1	Neosynephrin, 1 cc.	32.9	37.3	Hypodermic more effective.
		1	Epinephrin, 1 cc.	28.6	42.2	
		1	Epi., hypo., 1 cc.	34.7	51.9	
M. K.	Ayerza's disease	1	Neosynephrin, 1 cc.	24.0	30.2	Reaction after hypodermic.
		1	Epinephrin, 1 cc.	23.7	45.6	
		1	Epi., hypo., 1 cc.	16.4	62.4	
G. G.	Pulmonary fibrosis	1	Neosynephrin, 1 cc.	..	..	Cough easier after neosyn.
		1	Epi., hypo., 1 cc.	13.9	14.6	
K. B.	Emphysema	1	Neosynephrin, 1 cc.	15.3	19.7	Reaction after any epinephrin.
		1	Epinephrin, 1 cc.	15.3	18.4	
C. G.	Emphysema	1	Neo.-epi., 1 cc.	13.8	20.9	Marked relief from spray.
		1	Epi., hypo., 1 cc.	13.8	21.6	
B. S.	Emphysema	1	Neosynephrin, 1 cc.	23.1	31.1	Reaction after any epinephrin.

The continuous inhalation technique has also been employed successfully in a number of cases of acute bronchiolitis or bronchopneumonia when this has been accompanied by symptoms of obstructive asthma. During the past season several cases of the so-called non-bacterial, or "virus" or "acute interstitial" pneumonia (Reimann<sup>9</sup>) developed such symptoms; in 3 of which the spray was used with marked relief.

One case may be cited briefly. The patient was a young man of 31. Following an acute febrile onset, he became progressively worse for 2 weeks, the major condition being apparently a bronchiolitis with widespread patchy pneumonitis. It extended throughout both lungs, except for a small region in the right upper lobe. Symptoms were fever, weakness, severe racking cough, asthmatic dyspnea, extreme cyanosis. He was in an oxygen tent with an oxygen concentration of 60 to 70%, but still dyspneic and cyanotic. An extra oxygen tank was placed beside the bed, a long rubber tubing connection extending to the vaporizer which was inside the tent. Whenever desired, the spray could be turned on and inhaled without modifying oxygen treatment, and without any extra exertion on the part of the patient. This spray was used, with Vaponefrin as bronchodilator solution, 10 or 12 times a day, with marked relief to dyspnea, asthma, and cough, and no constitutional side-effects. It was of particular value in helping the patient to raise sputum. In the third week, the pneumonia began to resolve, the temperature decreased, and the patient gradually improved.

From the tables, no consistent indication can be obtained as to the relative effectiveness of the various solutions. From clinical observation it appeared that epinephrin 1:100, and Vaponefrin, usually had the strongest action, and neosynephrin the weakest; just as Graeser points out in his recent report.<sup>3</sup> The action of the epinephrin-neosynephrin mixtures seemed to have no special advantages or disadvantages. In some instances, epinephrin hypodermically, 1 cc. of 1:1000 solution, was more effective than any of the sprays (Table 2).

With respect to undesirable side-effects, neosynephrin had none whatever, in any patient, even on prolonged use. Epinephrin not infrequently caused the dryness and irritation of mucous membranes, and occasionally the constitutional side-effects that have been reported with the use of the hand-bulb atomizer and deep inhalation. The continuous inhalation technique did not appear to increase these toxic effects.

From experience thus far obtained, it would appear that the continuous spray technique has two general indications:

1. In severe asthmatic states, to relieve exacerbations of symptoms at intervals through the day; either supplementing ephedrin or hypodermic epinephrin in this respect, or replacing such medication if the subject has become resistant.

2. In cases of chronic fibrosis and emphysema, when they are confined to bed, or on a limited ambulatory régime; for relief of dyspnea, asthma, and cough. In such cases the most effective régime is often to use the spray at regular intervals throughout the day, as well as at other times as needed for acute asthma and cough. A convenient schedule is to inhale the vapor of 0.5 cc. to 1.5 cc. of solution for 4 to 10 minutes (1) on waking in the morning, and before getting out of bed, (2) in the middle of the day, *e. g.*, after lunch, (3) just before retiring at night. Often continuous inhalations of this kind may be supplemented by the use of the hand-bulb vaporizer when the patient is up and about. Our experience corresponds with that of Graeser, that neosynephrin used with the hand atomizer is ineffective.

Epinephrin 1:100 or, preferably, Vaponefrin solution will usually be most effective with the continuous technique, unless there are local or constitutional side-effects; in such instances, continuous neosynephrin inhalations may bring relief.

**Summary.** 1. A method is described for providing continuous vaporization of solutions of bronchodilator drugs, for use as oral inhalation in asthmatic and emphysematous subjects.

2. This technique often provides more effective inhalation therapy in very ill or dyspneic patients, using 1:100 epinephrin, or Vaponefrin solution than is obtained by the hand-bulb, and with much less effort on the part of the patient.

3. Some patients who were sensitive to 1:100 epinephrin, could



obtain symptomatic relief by neosynephrin 1:100, when this was given by the continuous inhalation technique. The neosynephrin solution, while usually weaker in its action than epinephrin 1:100, was entirely free from undesirable side-effects.

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### ON THE QUANTITATIVE RELATIONSHIP BETWEEN CHLORIDE AND SODIUM EXCRETION IN THE URINE.

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SIEDECK and Zuckerkandl<sup>8,9a,b</sup> have found that the ratio of Na:Cl in the urine varied on different days, but insignificantly (0.95 to 1.03) in healthy persons who received ordinary food while staying in bed. Deviations from this value, therefore, as found in several diseases ("serous inflammation") were thought to give rise to far reaching conclusions. They also direct attention to typical differences of the Na:Cl ratio in day and night urine, a matter that is related to our investigations on the different ions in cases of nycturia (Mainzer,<sup>3a,b</sup> Mainzer and Hersch<sup>4a,b</sup>). In 50 day and night urines with normal fluid output and in 50 nycturic urines we determined the sodium, potassium and chloride concentrations from 13 persons in whom there were no other diseases likely to influence the water and salt metabolism. Five of these persons had been for some weeks convalescent from acute infectious diseases. All received the ordinary hospital food with salt at random, and were kept in bed.

**Methods.** The following methods were used in carrying out the analyses: The chlorides were determined by means of titration (according to Mohr and our own micromethod). Calcium, magnesium and the phosphates were removed (according to the method described by MacKay and Butler; cf. Peters and van Slyke<sup>5a</sup>), in order to determine the proportion of Na and K. In the filtrate the total bases were determined (after the method of Stadie and Ross<sup>10</sup>) as sulphates. Following ignition of the urine according to Stolte, Na was precipitated according to the method described by Kramer and Gittleman,<sup>1</sup> modified by Eisenman, as pyroantimoniate and determined iodometrically.

The balance (total bases minus sodium) indicates the potassium concentration (after precipitation of the alkaline earths, as mentioned above). We prefer this indirect method of determining the potassium concentration to the usual direct microdetermination, according to Kramer and Tisdall,<sup>2</sup> since after several years' experience, we agree with the statement of Peters and Van Slyke,<sup>5b</sup> that the latter is not entirely satisfactory. Specific gravity was also ascertained, and the hydrogen-ion concentration determined by means of Michaelis' indicators.

A discussion of our results, as they concern the ratio Na:Cl follows.

TABLE 1.—VALUE OF THE QUOTIENTS Na:Cl IN THE URINE.

Subject.	Number of specimens.	Quotient Na:Cl.			Number of specimens with a quotient Na:Cl = >1.10. 19	Number of specimens with a quotient Na:Cl = <0.90. 23
		Lowest value.	Medium value.	Highest value.		
Normal urine	{ Day . . . . 50	0.54	0.99	1.02	1.56	42
	{ Night . . . . 50	0.43	1.04			
					16	21
					37	
Nycturic urine	{ Day . . . . 50	0.51	0.92	1.02	1.68	42
	{ Night . . . . 50	0.65	1.12			
					13	29
					21	21
					42	

Table 1 shows that there is no constancy (as held by Siedek and Zuckerkandl<sup>9a,b</sup>) of the ratio Na:Cl. In contrast to these workers, although working under the same experimental conditions, we encountered large variations of this ratio, between 0.43 and 2.81. On the whole, about four-fifths of our results were far from the point of equivalence, namely below 0.90 and above 1.10. This was so with reference to normal as well as to nycturic urines (with day as well as with night urines), between which there did not appear any significant difference, nor did the adjustment of the figures taken from day and night urine (which had been tested separately) produce any results on those lines. This is very clearly shown in Table 2. In more than half of the 100 pairs of urines which were analyzed, the deviation from the ratio Na:Cl = 1 as regards the day and night urines was in the same direction.

TABLE 2.—VALUE OF THE QUOTIENT Na:Cl IN THE URINE.

Subject.	Number of specimens.	Quotient of urine of the day as well as of the night.	
		Lower than 0.90.	Higher than 1.10.
Normal urine . . . . .	50	13	9
Nycturic urine . . . . .	50	19	13

The diagram gives a clear picture of the distribution of the different values of the ratio. The abscissa represents the ratio, the ordinate the relative frequency (per 100). In our diagram the figure 0.6 stands for all figures between 0.60 and 0.69, the figure 0.7 for 0.70

to 0.79 and so forth. The diagram is based on the analyses of all 200 urines. We did not take into account figures above 2, since they occurred extremely rarely.

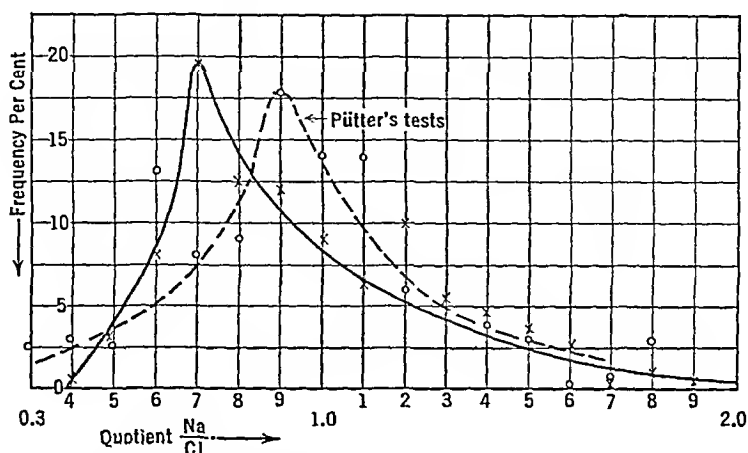


CHART 1.—Distribution of the frequency of the quotient Na:Cl in 200 personal tests (x—x) and in 35 Puetter's tests (o-----o). Abscissa : Quotient Na:Cl. Ordinate : Percentage of frequency.

The diagram shows a regular frequency curve with regard to the different values of the ratio. The distribution seems less regular if normal and nycturic urines are treated separately, in view of the smaller number of results available then, but on the whole both curves follow similar lines. The maximum frequency is not at 1, as should be expected in accordance with the preceding arguments, but between 0.70 and 0.79 (in the diagram represented by the figure 0.7). The curve of frequency declines in both directions, with regard to the higher as well as the lower values, so that the ratio 1 occurs about half as frequently as those around 0.75. The decline of the curve, however, is no symmetrical one, as should conform to the ideal variation curve of accidental deviation from the mean value (binomial curve). The frequency of the occurrence of a certain value of the ratio declines towards the figures below 0.7 much more rapidly than is the case in the increasing values above 0.7. From three-quarters to four-fifths of the chlorides, therefore, are, as a rule, excreted in the urine as sodium salts, the remainder in other compounds. Urines in which greater amounts of chlorides which are combined with other kations are present, show a very rapid decline in frequency, and the greater the amount of such chlorides the more this is so. Urines in which the excreted quantity of Na is larger than four-fifths of the chlorides show a much slower decline in frequency with increasing Na concentration. There are, therefore, under normal conditions comparatively many urines in which considerable amounts of Na are combined with phosphoric, sulphuric and carbonic acid.

It is owing to this peculiar unsymmetrical behavior of the frequency curve that the mean value of the ratio Na:Cl (in all groups which we formed [see Chart]) approaches the value 1, although practically half of the tested urines contain an amount of Na corresponding to but four-fifths of the excreted chlorides or even less.

On an average, in tests carried out over a long period, even according to our analyses, almost equal amounts of Na and Cl are excreted. This contradicts the argument that the low ratio of Na:Cl which we found in contrast to Siedek and Zuckerkandl is produced by an exceedingly high proportion of potassium in the food given by us—most of the calcium and magnesium being excreted through the intestine. Such a disproportion of the ion-supply would have become apparent, in particular, in the total result.

In view of this discrepancy between our results and those of the Austrian workers, we tried to find further analyses of this type in the literature. But it was not without difficulty, however, that we succeeded in finding sufficient material on the determination of the kations in the urine.

The classic paper of Salkowski,<sup>7</sup> still of fundamental importance today, was unfortunately not at our disposal in the original. But we found what we were looking for in 35 analyses\* of this kind performed by Puetter<sup>6</sup> on normal urines of a 24-hour period, though carried out from rather a different viewpoint.

The behavior of the ratio of Na:Cl (deduced by us from Puetter's analyses) is clearly illustrated by Table 3.

TABLE 3.—VALUE OF THE QUOTIENTS Na:Cl IN THE URINE. (PUETTER'S TESTS.)

Subject.	Number of specimens.	Quotient Na:Cl.			Number of specimens with a quotient Na:Cl = > 1.10.	Number of specimens with a quotient Na:Cl = < 0.90.
		Lowest value.	Medium value.	Highest value.		
Normal 24-hour urine	35	0.31	0.97	1.80	10	14

Puetter's investigations are in accord with our results: 1, the range of variation of the ratio Na:Cl is very large (0.31 to 1.80); 2, in two-thirds of the urines analyzed the ratio is very far from the value of equivalence = 1; 3, the average value taken from all urines very nearly approaches the value Na:Cl = 1.

Even Puetter himself stresses these points. After having reported on the relation between excreted chloride and the amount of kations (deduced from the mean value apparent in 32 analyses, taking also into consideration Na, K and  $\text{NH}_3$ ) he continues: "This proportion is by no means the same in all individual cases, sometimes less chlorine is excreted than should be expected considering the quantity of Na+K, sometimes more" (p. 24). In his opinion this results from the fact "that the ions . . . largely go their own way in the excretion process . . . that even if the intake of salt is

\* One of the analyses of this series was eliminated (AQ) since it was obtained after the administration of Na-bicarbonate.

as constant as is the intake of *e. g.*, nitrogen, the excretion of the ions and the salts is not at all as constant as that of urea" (pp. 37, 38).

In contrast to the agreement between our findings and Puetter's analyses—insofar as the small number of his analyses permits a conclusion—the curve of frequency of the ratio is symmetrically arranged around the mean value in Puetter's investigations, while in ours it is not. The corresponding curve, given also in the Chart drawn according to the principles mentioned above gives clear evidence of this fact.

The deductions to be drawn from our analyses as regards the ratio of Na:Cl in the urine are, therefore, fully confirmed by Puetter's findings and are included in the following statements:

1. With normal intake of food (the patients remaining in bed in our experiments) the ratio of Na:Cl varies greatly in the urines collected in 12-hour (day and night urines) as well as 24-hour periods (0.31 to 2.81). That means that the chlorides appear in combination with Na-ion and as salts of other kations (K,  $\text{NH}_3$ , Ca, Mg) and that, on the other hand, the Na-ion is present combined with acids other than hydrochloric (phosphates, bicarbonates).

2. Tests carried out over a long period, however, reveal that under above conditions,  $\text{Na}^+$  and  $\text{Cl}^-$  are excreted in practically equivalent quantity.

3. With regard to the distribution of the frequency of their occurrence the urines can be grouped in a curve around a maximum value in such a manner that three-quarters to four-fifths are at a great distance from the point at which the excretion of  $\text{Na}^+$  and  $\text{Cl}^-$  occurs in equivalent quantities (Na:Cl = 1).

**Conclusions.** In view of these facts, the attempts to draw clinical conclusions from the behavior of the ratio of Na:Cl seems to us justified only insofar as prolonged experimental periods are considered, in accordance with the classic principles of metabolic physiology.

The short-term experiment, which uses ratios obtained on some individual days, only permits of conclusions—if ever—when the amplitudes observed—their extent and regularity of appearance—convince us that they are by no means spontaneous, such spontaneous variations being the rule according to Puetter's and our own analyses.

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## ON THE DANGER OF FORCING FLUIDS IN MALNUTRITION.

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SPONTANEOUS edema is a well-known phenomenon of chronic malnutrition. Twenty-three hundred years ago Diogenes Laertius wrote that Heraclitus retired in disgust with mankind to the mountains, lived on vegetables and herbs alone, acquired dropsy and died.<sup>24b</sup> To bring a somewhat similar event to date, Mahatma Gandhi is reported in recent press dispatches to have acquired dropsy in his latest fast.

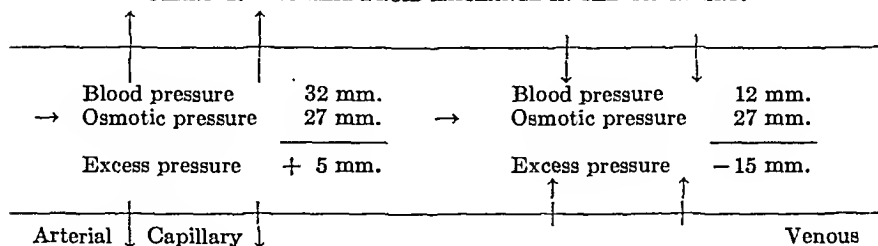
Malnutrition is often accompanied by a dry tongue which may or may not be a sign of dehydration. A diminished urinary output is a more reliable sign of true dehydration than a dry tongue which may be due to mouth breathing. But often without consideration as to the real presence of dehydration, the clinician's first thought is to order large amounts of fluid intravenously. The result may be massive edema, even acute pulmonary edema or eclamptic-like convulsions. The malnourished hypoproteinemic surgical patient is especially liable to such a catastrophe. The mechanism by which such edema may be forced on the malnourished patient is the lowered osmotic pressure within the capillaries brought about by low total plasma protein and plasma albumin accompanying malnutrition.

Our understanding of the mechanism concerned in this edema has progressed as follows:

Starling<sup>19</sup> in 1896 first suggested the relationship of intracapillary pressure tending to force fluid through the permeable membrane wall of the capillary, and osmotic pressure of the blood plasma attracting fluid back into the capillary. Then many cases of edema were recognized as due to malnutrition during the great war, but the mechanism of its production by hypoproteinemia and the resultant lowered plasma osmotic pressure was not generally realized. Next Epstein<sup>7</sup> in 1917 first actually suspected the lowered osmotic pressure of hypoproteinemia as the cause of edema in nephrosis. Others soon applied this idea to cases of nutritional edema, spontaneous cases in America, famine cases in China,<sup>11,12,17,24a,25a,26</sup> and proved again and again the actual presence of low plasma proteins and albumins in such cases. Barker<sup>2</sup> proved the thesis by plasmapheresis experiments in dogs producing massive edema.

The actual mechanism of edema production in the hypoproteinemia of malnutrition may be diagrammed simply modified after Myers.<sup>16</sup>

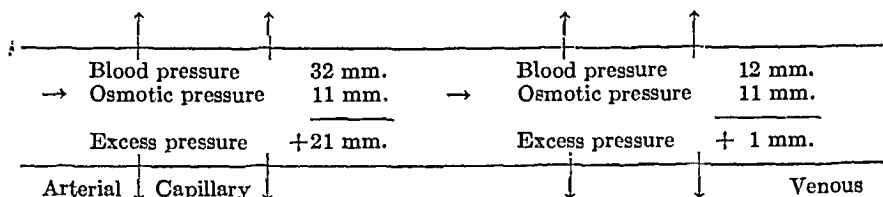
CHART 1.—NORMAL FLUID EXCHANGE IN THE CAPILLARY.



While the above explanation offers the background for the development of edema in malnutrition, other precipitating factors are of the utmost importance. Landis<sup>10</sup> mentions as contributing factors high salt and high fluid intake which will precipitate or increase edema only if both are available, the salt being necessary to fix the fluid in the tissue, and an excess of fluid being necessary to join the salt to form edema.

CHART 2.—EDEMA OF SERUM ALBUMIN DEPLETION.

- (1) of nephrosis—excessive loss in urine
- (2) of malnutrition—impaired formation or inadequate intake



In clinical practice a combination of malnutrition with unsuspected hypoproteinemia and a dry tongue may seem a prime indication to administer large amounts of glucose in saline. Due to specific protein starvation hypoproteinemia may be present even in the obese patient. The result may be disastrous as in the following case report of an apparently well nourished patient:

CASE 1.—Mrs. J. M., aged 33, entered the hospital on December 17, 1938. Her entrance complaints were anemia and lack of energy of 3 years' duration. Three years previous to admission she was delivered of a normally developed dead baby at term by low forceps, and sustained a third degree laceration, the repair of which rendered intercourse impossible. During her postpartum course she was found to have a pyelitis and anemia with hemoglobin of 30%; red blood cells 2,000,000. While in the hospital she became completely devoid of hair. Only the hair on her head came back sparsely. In the Spring of 1938 a basal metabolic rate was -37%. For the last 3 years she had been having spells of coma which lasted 8 to 9 minutes. For these she had been given glucose and normal saline solution subcutaneously by her home doctor. She had had 5 such attacks in the past year. There was no biting of the tongue or convulsive movements.

There was evidently a considerable psychic factor connected with the episodes of unconsciousness, the patient always staging the spells as her husband was about to enter the house. She had been vomiting for the past year off and on, 3 to 4 times a week the past 2 weeks. The loss of her baby, the impossibility of intercourse, her loss of hair all contributed to her marked melancholy. She was given liver extract, and had been taking an unknown amount of iron and 3 grains of thyroid extract daily for about 9 months, all without improvement.

Family, past medical and social histories were irrelevant. Before we saw her in consultation she had been given an emergency transfusion of 500 cc. of blood and 3500 cc. 5% glucose in normal saline intravenously within 36 hours.

*Physical examination* after these fluids were given revealed an anemic appearing white female, fairly well nourished who talked slowly and appeared mentally sluggish. Blood pressure was 100/60. The head and neck were normal except for pallor of the mucous membranes, absence of eyebrows and eyelashes, and puffiness of the face. The heart was normal. The pulse rate of 92 on entrance had jumped to 110. There were many moist râles heard throughout both lung fields. The solid abdominal organs were not palpable. There was a pitting edema of both upper and lower extremities as well as over the sacrum. Pubic and axillary hair was scanty.

*Laboratory findings:* The red blood count, white blood count and hemoglobin were 3,470,000, 10,000, and 55%, respectively. The differential count showed filaments 12%, non-filaments 16%, lymphocytes 59%, monocytes 5%, eosinophils 6%, and basophils 2%. The red blood cells appeared hypochromic in the smear. The Kahn test was negative. On December 19 the non-protein nitrogen was 25 mg., blood carbon dioxide 25 vols.%, blood chlorides 340 mg., blood calcium 8.6 mg., blood cholesterol\* 122 mg., total serum protein 6.58 gm., serum albumin 2.91 gm., serum globulin 3.67 gm., albumin globulin ratio 0.8. The low non-protein nitrogen, blood calcium, cholesterol and plasma proteins were probably due to hydremia following 7900 cc. of intravenous fluid in the preceding 36 hours. An uncatheterized specimen of urine was acid, specific gravity 1.015, + albumin, no sugar, acetone or diacetic acid; sediment examination revealed many pus cells, some in clumps, no red blood cells and a few granular casts. The daily urinary output was 150 cc., 750 cc., 350 cc., and then the patient had involuntary urination.

This patient received 7400 cc. of 5% glucose and normal saline in 36 hours. Blood (500 cc.) was given on the day of admission without reaction. Following this the patient developed pulmonary edema and generalized anasarca. On December 20 a duodenal tube was passed and high protein vitamin feedings administered. She was also receiving thyroid, gr. 1, three times daily, cortin, 12 cc. in 2 days, 1 cc. anterior and 0.5 cc. posterior pituitary extract. Her temperature rose to 103.4° on that day, and she expired rather abruptly. Autopsy was refused.

*Differential diagnosis:* Simmonds' disease is a possibility, but seems ruled out by the absence of any cachexia 3 years following the loss of her hair. Anorexia nervosa is more likely considering the psychic background and hysterical character of her so-called fainting spells. Myxedema must be considered with the low basal metabolic rate of -37%, but she did not have low temperature, slow pulse, coarse features, obesity, high blood cholesterol or response to 3 grains of thyroid extract daily for 9 months. We feel it more likely that the hair loss at the time of her delivery was due to the fever of pyelitis of pregnancy, and the psychic shock of a stillbirth.

Our final diagnoses were malnutrition with edema and acidosis; pul-

\* Method of Myers and Waidell in Peters and Van Slyke: *The Williams & Wilkins Company*, Baltimore, 2, 506, 1932.



monary edema; terminal bronchopneumonia; anorexia nervosa; pyelonephritis; hypochromic anemia; and question of myxedema.

**Comment.** It will be noted in this case that the serum protein and albumin were comparatively high (6.58 gm. and 2.91 gm. per 100 cc., respectively) where Moore and Van Slyke<sup>15</sup> assert the usual critical level for the appearance of edema is 5.5 gm. total serum protein and 2.5 gm. serum albumin. One must also bear in mind the predominant rôle of albumin which, being the smaller molecule, exerts the greater osmotic pressure. The loss of albumin, therefore, is of greater import than the loss of other serum proteins. Therefore neither the total protein figure nor the albumin-globulin ratio is of as great importance as regards formation of edema as a low absolute albumin content of the blood plasma. Peters and Eisenman<sup>17</sup> affirm that administration of large quantities of fluid and salt may cause edema to appear at colloid pressures higher than those at which it is usually encountered in nephrosis or plasmapheresis experiments. Youmans<sup>25b</sup> states that in severe cases of nutritional edema the lowered osmotic pressure is the prime factor in the production of edema, but in milder cases with only slight hypoproteinemia secondary factors play an important rôle. The secondary factors precipitating the edema may be posture, the intake of salt and water, environmental temperature, tissue tension, and to this list we might add beriberi. Supported by Weech and Ling,<sup>22</sup> and by Falta and Quittner,<sup>8</sup> Youmans makes the statement, "salt and water are of course necessary for the formation of edema, and within certain limits the giving or withholding of them may cause edema to appear or disappear or modify the amount of edema." These secondary factors often belie the so-called "critical level."

The large amount of salt and water administered before this case was recognized as one of relative hypoproteinemia was undoubtedly the factor precipitating massive edema including fatal pulmonary edema. Weech, Goettsch, and Reeves<sup>23</sup> fed large amounts of salt and water to dogs already rendered hypoproteinemic and found "an augmentation of fluid in the interstitial reservoir" due to a fall in serum proteins enough to cause an average decline of 17 or 20 mm. of water in the colloid osmotic pressure of the serum. They also feel salt and water ingestion causes an augmentation of plasma volume of about 10% and suggest that this increase may be associated with a rise of capillary blood pressure, a further cause for "augmentation of fluid in the interstitial reservoir." The increased fluid volume in the vascular bed and consequent rise of capillary blood pressure constitutes hydremic plethora. It is more probable that the pulmonary edema in our case was caused by the increased capillary pressure due to increased blood volume with left-sided failure. Pulmonary edema is not an occurrence in cases of pure hypoproteinemia as produced in plasmapheresis experiments, nor does it commonly occur in nephrosis.

Weech and Ling<sup>22</sup> gave salt and soda bicarbonate to 2 cases of nutritional edema, and found such feeding caused a marked retention of water and edema, with a retention of chlorides. They concluded the cation sodium was the important element causing the retention of fluid. In one of these patients after a normal serum protein had been restored the edema could not be reproduced by ingestion of large amounts of sodium and water.

Lowenburg and Miller<sup>13</sup> described a nutritional edema in a child due to gastro-enteritis and aggravated by a diet of glucose containing fluids, but no milk, and zwieback (poor in protein). Furthermore, she received 2 hypodermoclyses of 250 cc. of Hartman's solution (which contains NaCl) with consequent development of general anasarca. The child's serum protein was 3.5 gm., serum albumin 2.2 gm. per 100 cc. A high-protein, low-salt diet, and 5% sucrose as a diuretic rapidly reduced the edema and raised her serum proteins.

The following table from Youmans<sup>25b</sup> summarizes the effect of salt added to the diet in cases of nutritional edema:

TABLE 1.

Case.	Added salt.	Weight.		Edema.		Remarks.
		Before, kg.	After, kg.	Before.	After.	
L. E.	9 gm. daily for 4 days	66.3	67.7	0	++++	Legs sore and tender
F. I.	4 gm. daily for 10 days	78.4	80.5	0	++	
	After 8 days of low salt diet		78.8	++	=	
W. J.	10 gm. daily for 5 days	56.5	57.7	+	++++	Legs sore

Another secondary factor precipitating edema in hypoproteinemia is the anemia present in this patient which is known to cause increased capillary permeability. Peters and Eisenman<sup>17</sup> found that in malnourishment with anemia edema appears at higher osmotic pressures than in malnutrition without anemia. Quoting them, "Anemia increases the tendency to edema, and raises the albumin and osmotic pressure at which it may be expected to 4% and 26 mm. Hg, respectively."

The presence of an evidently good state of nutrition as regards the preservation of a good panniculus adiposus, or even obesity, should not throw the clinician off his guard, given a history of imbalanced diet, diarrhea, or vomiting, for even then hypoproteinemia may exist. "The serum protein depletion, like the body protein loss from which it arises, can be retarded and mitigated by the administration of large quantities of fat and carbohydrates; however, regeneration of the serum proteins can be accomplished only when enough protein is added to the diet to permit restoration of the previously wasted body protein. It would seem quite possible under these circumstances for both body protein depletion and hypoproteinemia to coexist with obesity in subjects who had undergone wasting with

an inadequate protein intake, either for therapeutic purposes or in the course of disease."<sup>17</sup>

The low basal metabolic rate in our case is not to be considered as *prima facie* evidence of hypothyroidism, as it is a common finding in undernutrition, and thyroid therapy in the past had not ameliorated the condition of this patient. Weech<sup>21</sup> quotes Denel and Ling as reporting cases of nutritional edema with basal metabolic rates of  $-5\%$  to  $-26\%$  with an average of  $-16\%$ . One must point out the greater significance of a low metabolic rate in an undernourished patient before edema has occurred. After edema has occurred there is a falsification of standards due to the increased weight of the patient.

CASE 2.—Mrs. M. M., aged 58, entered the hospital on December 27, 1937, complaining of diarrhea and vomiting. She said she had lost 45 pounds in weight during the past year, and had been bed-ridden for the past 4 months. Because she vomited most of her solid intake the patient was on a diet consisting chiefly of liquid foods. She had had a diarrhea for 3 weeks prior to admission, with 3 to 6 bowel movements per day. The stools were greenish-gray with no tarry substance or gross blood.

Past history, family history, social history were irrelevant.

*Physical examination* revealed an emaciated, small female, very ill-appearing but cooperative. There was no pigmentation of the skin. The eyes, ears, nose and throat were normal. The tongue was dry. The right lobe of the thyroid was enlarged, firm and uniform in consistency. Heart, lungs and abdomen were normal. The blood pressure was 80/42, 82/68 and 90/60 on 3 separate days.

*Laboratory findings:* The red blood cells were 4,640,000; hemoglobin, 55%. A catheter specimen of urine was acid, contained ++ albumin, no sugar or acetone. The microscopic examination of the urinary sediment revealed many white blood cells, many bacilli, and an occasional hyaline cast and red blood cell. A culture of the urine was positive for *B. coli*. The stool examination showed no occult blood. The Kahn and Mantoux tests were negative. The phenolsulphonephthalein test showed 5% excretion in 1 hour. Fluid output varied from 80 cc. to 70 cc. the first 2 days, later increasing to 975 cc. after the intravenous administration of fluids and the disappearance of dehydration.

Roentgen examination of the upper abdominal region revealed a shadow overlying the transverse process of the third lumbar vertebra suggesting a calcium deposit in the right adrenal. Stereoscopic roentgenogram of the chest revealed an old primary tuberculous complex.

*Progress.* Examination of the gastro-intestinal tract with barium showed a marked duodenal stasis. This was relieved by having the patient lie in the right oblique prone position. She was tube fed, and gradually improved. The diarrhea was stubborn at first, but gradually cleared. She was given 1000 cc. saline intravenously every day for 7 days with 10 cc. cortin. She received 3 gm. salt by mouth in capsules daily. A marked peripheral edema developed. This improved under diuresis by mercupurin and acid salts. The blood pressure increased from 80/42 to 124/70. At the height of her edema the patient developed eclamptic-like convulsions. She also developed an acute cystitis while in the hospital which was treated and improved. She was discharged against advice when a jejunostomy was proposed to enhance protein feeding. The vomiting together with the edema and convulsions continued at home. The patient finally died following a convulsion 3 months after discharge. A serum protein obtained at the patient's home showed a further drop after improvement in the hospital. Autopsy could not be obtained.

TABLE 2.—DATA IN CASE 2.

Date.	Dec. 28.	29.	30.	31.	Jan. 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	Feb. 22.
Fluids i-v, cc. saline .	2000	2000	500 blood	1000	1000	1000	1000+ 500 of blood 67.44	1000	Edema noted	..	..	..	Diuretic régime started	85.5	84.5	76.5	75	74.5	74	
N.P.N. . . . .	105.6	..	..	108.08	..	..	..	..	..	..	49.98	..	..	..	44.79	..	60	..	..	
Blood chlorides . .	330	..	..	410	..	..	..	430	..	..	470	..	..	..	440	..	..	..	..	
Total proteins . .	..	..	..	..	..	..	..	..	..	..	..	4.887	..	..	6.233	..	5.888	..	..	5.035
Serum albumin . .	..	..	..	..	..	..	..	..	..	..	..	2.373	..	..	2.148	..	2.342	..	..	1.719
Serum globulin . .	..	..	..	..	..	..	..	..	..	..	..	2.514	..	..	4.085	..	3.546	..	..	3.316
A/G ratio . . . .	..	..	..	..	..	..	..	..	..	..	..	0.94	..	..	0.5	..	0.65	..	..	0.51
Weight, pounds . .	..	..	..	..	68	..	..	..	89	89.5	87.5	87.5	86.5	85.5	84.5	76.5	75	74.5	74	

Final diagnoses: Addison's disease; edema of hypoproteinemia and malnutrition; primary pulmonary tuberculous complex; chronic pyelitis; acute cystitis; hypochromic anemia; mesenteric pedicle compression with duodenal stasis; non-toxic nodular goiter.

**Comment.** This case points out the danger of salt and water therapy pushed too far in Addison's disease. While there was marked rise in blood pressure, blood sodium chloride and the general clinical improvement usually seen in Addisonian crisis on this type of therapy anasarca and eclamptic-like convulsions suddenly intervened. The analogy between this patient's convulsions and those of eclampsia is striking in view of the newer knowledge concerning the cause of the latter. Strauss<sup>20</sup> observed that true toxemia of pregnancy often accompanied by eclamptic fits was associated with hypoproteinemia with a significant gain in weight, edema and hypertension when soda was administered either as the chloride or bicarbonate. Arnold<sup>1</sup> also attributes eclampsia with its convulsions to fluid imbalance. Herden<sup>9</sup> believes that protein stabilization treatment has dealt with fundamental factors in the prevention of eclampsia. de Snoo<sup>18</sup> states that salt retention in the tissues is the true cause of eclampsia which is another way of indicting fluid imbalance.

The persistence of edema in this patient after improvement in her serum proteins may be partly attributed to another secondary factor in the cause of edema; namely, tissue distention once edema has been extreme. Weech<sup>21</sup> again states that in malnutrition the resistance of the connective tissue network may be impaired. A chronic distention of this network therefore may account for persistence of edema after the plasma osmotic pressure has been restored to normal.

The same author is authority for the statement that the blood cholesterol is normal in nutritional edema as contrasted to nephrosis. It will be noted that the blood cholesterol was within normal limits in our patient.

**CASE 3.**—Miss A. S., aged 38, a well-nourished female, was brought to the hospital with a diagnosis of acute intestinal obstruction. At exploration the day of admission a carcinoma of the hepatic flexure was disclosed. A lateral anastomosis was done. The patient was given 2000 cc. of 5% glucose in saline intravenously immediately postoperatively. The following day she was given 4000 cc. of 5% glucose in saline solution intravenously. At that time it was noted that she was developing generalized edema.

**Laboratory findings:** Total serum protein determined at the onset of edema 2 days after entry was found to be 4.711 gm., the serum albumin was 2.820 gm., and the serum globulin was 1.891 gm. The A/G ratio was 1.4.

The patient was given blood transfusions of 500 cc. each on the second and fourth postoperative days. On the fifth postoperative day all clinical edema had disappeared. She expired on the seventh postoperative day. At autopsy, peritonitis was found to be cause of death.

**CASE 4.**—Mrs. F. S., aged 34, was a patient in the hospital for 10 months. She had a recto-vaginal fistula, attempts for the repair of which had been made on two occasions. Following her second operation she was given 1000 cc. of 5% glucose in normal saline daily for 10 days. She developed an edema over the sacrum and a peripheral edema.

Laboratory findings: Total serum protein at the onset of edema was found to be 5.3 gm., the serum albumin was 3.3 gm., and the serum globulin 2 gm. The A/G ratio was 1.6.

The intravenous injections of 5% glucose in saline solution were discontinued with the onset of the edema and 5% glucose in distilled water was substituted. On this regimen the edema gradually subsided.

**Comment.** More warnings have been sounded in the medical literature concerning the danger of over-pushing intravenous fluids in postoperative cases than in medical cases of malnutrition. Collier, Frederick, Dick and Maddock's<sup>5</sup> monumental work on water balance lays the foundation for proper treatment of such cases. They have pointed out the necessity of a judicious choice between glucose in distilled water and saline solution administration when further administration of saline infusion may result in salt and water retention. It is interesting to note that the edema of Case 3 disappeared on administration of blood transfusions; and in Case 4 on switching from saline solution to 5% glucose in distilled water.

Meyer<sup>14</sup> reported a patient who developed massive, fairly generalized edema after an abdominal operation which could be easily and logically explained upon the basis of undernutrition, protein loss through purulent drainage, and dilution of serum proteins by the administration of large quantities of salt and water in the form of normal saline. He points out the possible danger of causing pulmonary edema in pushing fluids in such cases. Beard and Blalock<sup>3,4</sup> have also warned of the same danger of edema by postoperative fluid therapy diluting the serum proteins.

The authors have had no experience with the intravenous administration of amino-acids, but the method recently reported by Elman and Weiner<sup>6</sup> offers great promise of being an ideal solution of the necessity to correct the serum protein level before dehydration can be safely corrected in these cases.

**Conclusions.** 1. A low fluid output is a better sign of dehydration than a dry tongue.

2. The hypoproteinemia of malnutrition constitutes a contraindication to the administration of large amounts of salt and water parenterally, despite the fact the patient may appear to be dehydrated.

3. The serum proteins must first be reestablished to normal before attempting to correct dehydration or massive edema, fatal pulmonary edema, or eclamptic-like convulsions may supervene.

4. Too much salt and water intravenously in cases of malnutrition precipitates an edema already potential by reason of the lowered osmotic pressure of hypoproteinemia. Hydremic plethora with its increased intracapillary pressure further conditions the organism for the precipitation of acute pulmonary edema.

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## SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT.

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SEASONAL variation in the susceptibility of the respiratory tract to infection in northerly climates is well known. Hitherto, most research on this problem has been directed at the pathogenic organisms and the pathologic processes involved. There is little information pertaining to the reason why the respiratory tract is more easily invaded by these organisms at certain seasons of the year. The present work was undertaken with the idea of measuring, at different seasons of the year, something which might be considered as an index of the function of the respiratory tract. The work was done on animals housed under conditions of heat and humidity which may be considered somewhat similar to those of the average human population of this district.

The water content of the trachea and of the bronchial and alveolar regions of the lungs was measured as an index of the function of these tissues. It was concluded on theoretical grounds and later proven by experiment, that the water content of tissues lining the respiratory airway must be finely adjusted. The cells lining the respiratory airway are continuously subjected to the passage to and fro of air, air which is warmed to body temperature and which

usually enters the body with insufficient moisture to saturate it at body temperature. The air passages are thus constantly fanned by dry, hot air. Some moisture is added to incoming air as it passes through the nasal cavity. If not sufficient, then further water must be evaporated from the cells lining the trachea, bronchi and smaller air passages. If any water so removed were not soon replaced, these tissues would dry up and become lifeless. That such does not occur is seen in the fact that animals and man may live for considerable periods—possibly indefinitely—when air is side-tracked from the nose and enters by way of a tracheotomy tube.

On the other hand, it is equally as important that too much secretion of water by these cells be prevented. If such occurred, the very fine air passages might become filled with a watery medium and the animal or person drown in its or his own secretions.

On these theoretical grounds, we concluded that there must be a fine adjustment in the water content of pulmonary tissues. If such were so, then one might find a relatively constant water content in these same tissues. This was determined experimentally to be the case. Being reasonably certain that water content could be taken as an index of function of these tissues, we proceeded to measure water content over a period of 1 year.

**Method.** The object of the procedure adopted was to measure the water content of different regions of the respiratory tract of laboratory animals under conditions which might be regarded as nearly normal as possible. The animals were housed in quarters wherein the temperature and humidity were the same as those to which persons working in the laboratory were exposed. They were allowed to drink and eat as they wished. The white rats were fed Purina Fox Chow Checkers; the guinea-pigs, alfalfa and fresh vegetables; and the cats, milk, bread and meat. The animals were killed without anesthesia by a light, stunning blow on the head followed by severing the cervical spinal cord with snippers. The thorax was then quickly opened, the trachea freed at the larynx and separated down to and including the lungs, keeping the tract free of as much blood as possible. Any adherent tissue was then removed and the whole divided into three parts. The trachea was one part. The distal third or half of each lobe of the lung constituted the second fraction which was termed the distal part or distal lung. The remaining parts of the lung were called the proximal part or proximal lung. A diagrammatic representation of these separated fractions is given in Figure 1. As described below, there was found to be a physiologic as well as an anatomic difference between the proximal and distal parts of the lung.

The separated fractions were quickly placed in separate, small, cleaned, dried and weighed weighing bottles with ground glass stoppers and the moist weight determined to the nearest 0.1 mg. They were then placed in a drying oven at 90° C. for 60 to 100 hours with the stoppers ajar. The stoppers were then inserted, the bottles cooled to room temperature and the dry weight ascertained. From these values the percentage of water in the original moist weight of tissue was calculated.

**Results.**—It was first necessary to establish whether the crude separation of the lobes of the lung gave fractions of significantly different water content. If such were not the case there would have



been little incentive to continue dividing the lung. A representative comparison of the respective percentages of water in the proximal and distal fractions of 11 young, 170-gm. rats is shown in Table 1. It will be noted that in all of the animals, the proximal part contained more water than the distal part. The mean difference was 1.6% of water with a standard deviation of 0.48 which is indica-

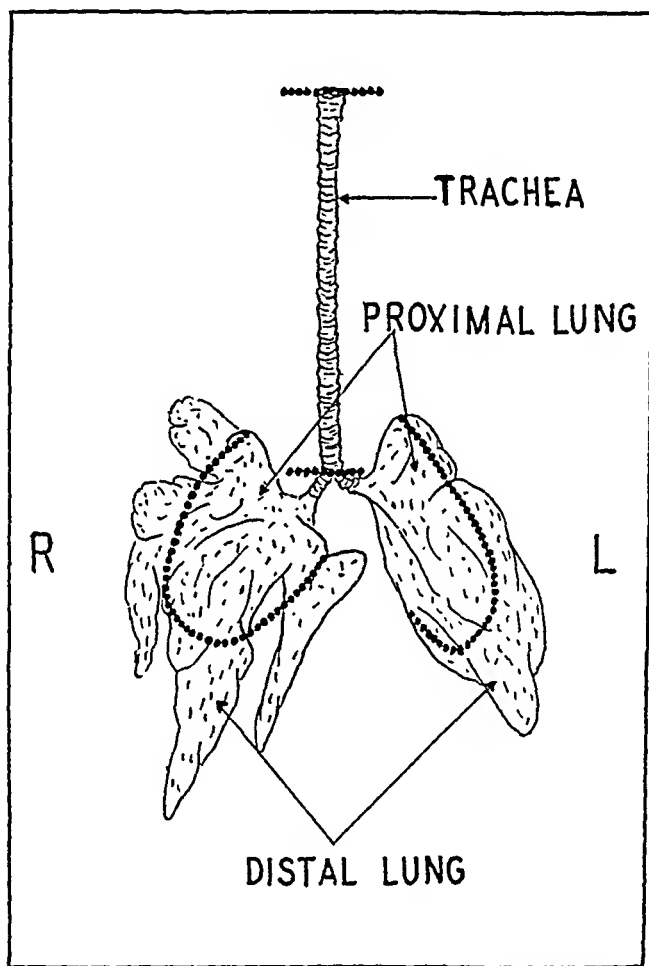


FIG. 1.—A diagrammatic representation of the separated fractions of the respiratory tract of albino rats.

tive of a statistically significant difference.<sup>3</sup> In certain other experiments, changes in water content were noted to affect one fraction and not the other. Hence it may be concluded that there is a significant physiologic difference in the two fractions of the lung as separated and this separation was thus used in subsequent work.

*The Constancy of Lung Water.* It has been suggested above that the water content of tissues composing the trachea and lungs must

be finely adjusted. If such were so, one might expect to find a relatively constant amount of water in such tissues. To investigate this, water percentages in representative groups of albino rats, guinea-pigs and in 2 cats were analyzed statistically and have been

TABLE 1.—THE WATER CONTENT OF A PROXIMAL AND DISTAL DIVISION OF THE LUNGS OF YOUNG RATS.

Rat No.	Per cent water.	
	Distal part.	Proximal part.
78 . . . . .	78.8	77.2
79 . . . . .	77.9	77.9
80 . . . . .	78.8	77.0
81 . . . . .	82.7	80.2
82 . . . . .	78.5	77.3
83 . . . . .	81.3	78.2
84 . . . . .	79.0	77.8
85 . . . . .	78.8	77.4
86 . . . . .	79.6	77.7
90 . . . . .	78.7	78.3
137 . . . . .	78.2	76.4
Mean . . . . .	79.2	77.6
Standard deviation . . . . .	1.4	0.91
Standard error . . . . .	0.40	0.26

presented in summary in Table 2. All values in each of these groups were obtained at the same season of the year and at times when abnormal variation, to be described later, did not occur.

Pearson's coefficient of variation<sup>3</sup> was used as a means of estimating and comparing the relative variation. Pearson's coefficient is

TABLE 2.—VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT OF ALBINO RATS WITHIN A GIVEN SEASON.

Value.	Per cent water.			
	Trachea.	Proximal part.	Distal part.	Whole tract.
<i>24 Albino Rats.</i>				
Mean . . . . .	74.3	78.7	79.5	78.8
Standard deviation . . . . .	3.6	0.91	0.89	0.73
Pearson's coefficient of variation . . . . .	4.9	1.2	1.1	0.93
<i>15 Guinea-pigs.</i>				
Mean . . . . .	64.2	78.4	80.1	76.9
Standard deviation . . . . .	12.2	1.3	3.4	3.8
Pearson's coefficient of variation . . . . .	19	1.6	4.3	4.9
<i>2 Cats.</i>				
Cat 1 . . . . .				81.3
Cat 2 . . . . .				81.8

the standard deviation divided by the mean and multiplied by 100; or, in other words, it is the standard deviation expressed as a percentage of the mean. In rats, the coefficient of variation of values for the water content of the whole respiratory tract and of the proximal and distal parts of the lung was remarkably constant at a value of about 1. The coefficient for the rat trachea was a good

deal higher, being 4.9. In guinea-pigs there was little variation in the water content of the distal part of the lung but considerable variation in the proximal lung and in the trachea.

For comparative purposes, variations in the water content of a number of tissues were collected at random from reprints on hand and Pearson's coefficient calculated. These comparative values have been given in Table 3. It will be noted that in general the coefficient is lowest for the lungs and that the only other body tissue approximating this constancy is the gray matter of the brain. On the other hand, the water content of the trachea is quite variable, relative to that of other body tissues. The coefficient of variation of other body constituents, for example lipids,<sup>1</sup> runs from 15 to 40 or more.

TABLE 3.—PEARSON'S COEFFICIENT OF VARIATION OF THE WATER CONTENT OF SEVERAL BODY TISSUES.

Tissue.	Animal.	Pearson's coefficient.
Respiratory tract (Table 4)	Rat	0.99
Distal lung—Tb. II	Rat	1.1
Proximal lung—Tb. II	Rat	1.2
Distal lung—Tb. II	Guinea-pig	1.6
Brain—gray matter (8)	Man	1.6
Uterine mucosa (5)	Pig	2.5
Brain—white (8)	Man	3.1
Trachea—Tb. II	Rat	3.6
Proximal lung—Tb. II	Guinea-pig	4.3
Gingival tissue (4)	Man	5.5
Teeth (2)	Man	18.7
Trachea—Tb. II	Guinea-pig	19.0

It is obvious from these remarks that the water content of the lungs is remarkably constant. These results would appear to substantiate the suggestion that the water content of lung tissue is under a nice control. Since the wide variation in guinea-pigs was found due to a bimodal distribution of results, the reason for which was not apparent, it was decided to continue the work using albino rats only.

*The Effect of Age.* The present work was begun with a group of older, mature albino rats weighing 300 gm. and continued with young rats weighing 150 to 200 gm. bred from the original stock. To ascertain if there was any difference in the water content of the respiratory tract of these two groups, results in 19 of the older animals were compared with results in 11 of the young rats, the water content being determined in both groups during June and July. There was no significant difference in the water content of the whole respiratory tract nor of the distal part of the lung but the trachea of the young rats contained slightly, but significantly, more water and the proximal part of the lung slightly but significantly less water than the corresponding parts of the older rats. The younger rats were used when they had reached at least 150 gm. in weight for the remainder of this work.

*Seasonal Variation.* As data accumulated, it became obvious that the water content of the respiratory tract was varying at certain seasons of the year. When the results for the whole respiratory tract were plotted according to the date on which they were obtained it became obvious that during the first cold spell of the autumn in September and October (early) when outside temperatures fell periodically to 60 to 65° F. and the laboratory had not yet been placed on regular and uniform heating, a considerable proportion of the water values were above normal. An opposite tendency to be below the normal range was seen in the results obtained from January to March after the animals had been exposed to a prolonged period of dry heat from a hot water heating system. This inference was drawn from the plotting of 120 determinations of the water content of the whole respiratory tract fairly evenly distributed over 11 months of the year.

In order to demonstrate these results, the mean of the entire group was calculated and was found to be 78.3% of water with a standard deviation of 1.16% of water. The results were then divided into periods of 5 weeks consecutively, such groups containing at least 10 animals. The number of animals in each 5-week period with water contents above the mean plus the standard deviation of the entire group was calculated. Also the number of animals with values below the mean minus the standard deviation was found and in each case the numbers were expressed as a percentage of the entire number of animals of the individual group. These percentages of cases above or below the range of the mean plus and minus its standard deviation were then plotted according to season in Figure 2.

The range of the mean plus and the mean minus the standard deviation includes two-thirds of all expected values. Of the remaining one-third of values, a half or one-sixth would be expected to lie above this range and one-sixth below it. Or 16.7% of a given distribution may be expected to lie above the stated range and 16.7% below it. This statistically *expected* variation is indicated in Figure 2 as a dotted area. Any variation beyond this dotted zone would not be expected in a random distribution of results. Yet in September and early October, 45 to 67% of values were above the range, given 3 to 4 times the expected variation above the range. Also in January, February and March, 50% of values were below the range showing again 3 times the expected variation below the range.

To prove that these changes graphically illustrated in Figure 2 were statistically significant, the data were divided into three groups. Group A included results obtained in September and early October, Group B those in January, February and March and Group C all other values. An analysis of the differences between these groups was then made and the results are given in Tables 4 and 5.

Table 4 presents data which demonstrate that when the unusual results in the early autumn and mid-winter are subtracted from the total cases, there remains a group of 71 cases in which the coefficient

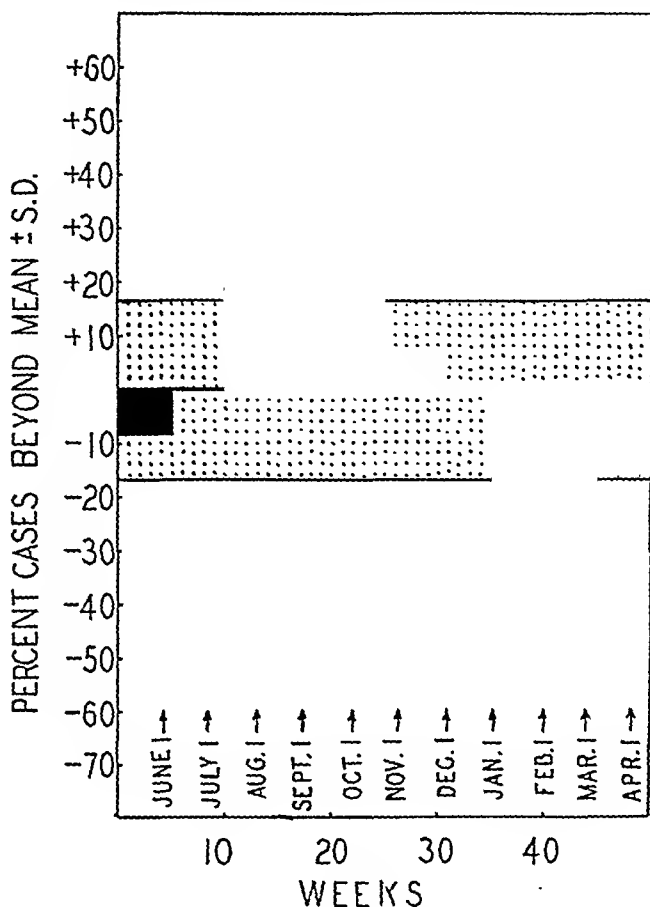


FIG. 2.—The percentage of cases, grouped in 5-week periods, showing more or less water than the range included by the mean plus and the mean minus the standard deviation. The dotted area represents the expected variation.

of variation is only 0.99. This demonstrates again that except for these two seasons, the water content of the rat respiratory tract remains exceedingly constant. In early autumn there was a rise in

TABLE 4.—A STATISTICAL ANALYSIS OF DATA, GROUPED ACCORDING TO SEASON, ON THE WATER CONTENT OF THE ENTIRE RESPIRATORY TRACT.

Group.	No. of cases.	Season.	Mean.	Standard deviation.	Standard error.
A . . . . .	35	Sept.-Oct.	79.7	0.88	0.16
B . . . . .	14	Jan. -Mar.	77.2	0.93	0.25
C . . . . .	71	All others	78.2	0.77	0.092

the water content of the respiratory tract from a mean of 78.2% to a mean of 79.7%. The mean difference of 1.5% of water was calculated to have a standard deviation of 0.19; the mean difference

was thus 7.9 times its standard deviation which is indicative of an overwhelmingly significance (Table 5). In the mid and late winter season, there was a fall in the water content from 78.2 to 77.2%, giving a mean difference of 1% of water which had a standard deviation of 0.27, the mean difference being 3.7 times its standard deviation and again overwhelmingly significant.<sup>3</sup> And, of course,

TABLE 5.—THE SIGNIFICANCE OF MEAN DIFFERENCES BETWEEN SEASONAL GROUPS OF TABLE 4: GROUP A—SEPT.—OCT.; GROUP B—JAN.—MAR.; GROUP C—ALL OTHERS.

Groups.	Mean difference.	Standard deviation of mean difference.	Mean difference
			Standard deviation.
A-C . . . . .	+1.5	0.19	7.9
B-C . . . . .	-1.0	0.27	3.7
A-B . . . . .	+2.5	0.30	8.3

there was a similar significant difference between the results in early autumn (Group A) and those in winter (Group B). These data conclusively demonstrate that there is a significant increase in the water content of the whole respiratory tract of white rats in early autumn and a significant decrease in winter.

*Seasonal Variation and Fractions of the Respiratory Tract.* An analysis of the data for each fraction of the respiratory tract was made in a manner similar to that for the whole tract which has been

TABLE 6.—THE SIGNIFICANCE OF THE EFFECT OF EARLY AUTUMN ON THE PER CENT WATER OF THE VARIOUS FRACTIONS OF THE RESPIRATORY TRACT.

Fraction.	Mean difference from normal.	Standard deviation of mean difference.
Trachea . . . . .	+2.8	1.2
Proximal lung . . . . .	+2.0	0.37
Distal lung . . . . .	+1.0	0.47

presented above. The effect of early autumn on the several fractions is analyzed in Table 6. All fractions of the respiratory tract were found to have significantly more water in the early autumn. The greatest increase occurred in the trachea, then in the proximal part of the lung and the least increase in the distal part of the lung.

TABLE 7.—THE SIGNIFICANCE OF THE EFFECT OF MID-WINTER ON THE PER CENT WATER OF THE VARIOUS FRACTIONS OF THE RESPIRATORY TRACT.

Fraction.	Mean difference from normal.	Standard deviation of mean difference.
Trachea . . . . .	-4.1	1.4
Proximal lung . . . . .	-0.5	0.39
Distal lung . . . . .	-1.9	0.24

A similar analysis of the water content of the fractions in winter revealed that there was a marked decrease in the water content of the trachea and distal fractions of the lung with no significant change in the proximal part (Table 7). Unfortunately, only 14 animals

were examined in the winter and the authors hesitate to attach too much significance to the differences between the distal and proximal parts of the lung.

**Discussion.**—The experimental evidence presented in this report proves that at most times of the year the respiratory tract of the albino rat contains a remarkably constant percentage of water. At two seasons, during the first cold spell of the autumn (to which the animals were exposed in an unheated building) and during the winter months in a hot water heated building, there occurred significant, abnormal changes. These changes invite the drawing of a corollary between them and the well-known preponderance of respiratory infections at the same seasons of the year. The comparison is more significant when it is recalled that these rats were housed under conditions which were probably similar to those under which the larger part of the human population in this district existed, with the exception that the rats did not go out-of-doors. The incidence of pneumonia reached its peak in Kingston at the time that these rats had the lowest water content in their respiratory tracts. It is a little more difficult to estimate the incidence of the common cold, bronchitis, laryngitis, and so on, since these are not reportable diseases. However, the absences of medical students from lectures reached peaks corresponding to the times of abnormal change in the water content of the rat lungs; at the same times the common cold and an epidemic of "influenza" were prevalent in Kingston and the data are offered for what they may be worth.

The present work would therefore suggest the possibility that infection of the respiratory tract may have as an etiologic factor, in addition to those known or believed to exist, a possible change in the physiology of the respiratory tract itself. It would appear that sudden chilling may alter the normal physiology of the respiratory tract and this possibility is being further investigated. Hot, dry air in artificially heated buildings may tend to dry the lung tissues to some extent and this alteration in lung physiology may account in part for respiratory infection in mid and late winter. *Apropos* of this, the observations of Rabinowitch<sup>6</sup> and Urquhart<sup>7</sup> are of interest: they state that respiratory infection is relatively uncommon among Canadian Eskimos who spend their winters in igloos in which the air would be probably fairly well saturated with moisture.

**Summary.** The percentage of water in the lungs of guinea-pigs and albino rats was found to remain remarkably constant. Pearson's coefficient of variation averaged about 1. In the albino rat, a significant increase in the water content occurred during the first cold spell of the autumn weeks and a significant drying of the respiratory tract took place in the winter in animals housed in a building heated by a hot water system. These changes affected all parts of the respiratory tract, especially the trachea and the proximal part of the lung in the autumn and the distal part of the lung in the

winter. The correspondence of these seasons to those in which respiratory infection is epidemic has been noted.

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### DISEASE AND THE NEGRO:

#### THYROID INVOLVEMENTS.

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FROM the relatively sparse literature on thyroid disease in the negro the idea was obtained that the condition was regarded as uncommon. We have investigated the situation naturally including a comparative study of the same condition among whites. Our hospital admissions are from a limited territory, representing families of employees of the Tennessee Coal, Iron and Railroad Company. For a number of years the relative proportion of whites and negroes in the employ of this company has been about 60% whites and 40% negroes. On January 1, 1938, there were employed 14,074 whites and 11,796 negroes. With this in mind, it is interesting to note that since the Employees Hospital was opened in November, 1919, to December 1, 1937, there have been 96 operations for thyroid disease in negroes against 133 operations for the condition in whites. Of the negroes, there were 8 males (9 operations) and 83 females (87 operations). Of the whites, there were 22 males (23 operations) and 101 females (110 operations).

Although the cases reported here do not comprise a very large group it is believed that they fairly represent similar conditions among the colored population of this County and State. They certainly present a definite comparison of the patients admitted to the Employees Hospital over a fixed period. It is logical to conclude that in Alabama thyroid disease is as relatively common in negroes as in whites.

The estimated population in the State of Alabama for the year 1937 was as follows: white, 1,857,522; negro, 1,021,440. A similar estimate for Jefferson County was: white, 295,000; negro, 182,100.



The normal capacity of the Employees Hospital is 310 beds and the yearly admissions, over a 10-year period, have been as follows:

TABLE 1.—WHITE AND NEGRO HOSPITAL ADMISSIONS.

Year.	Whites.	Negroes.
1928 . . . . .	4122	2701
1929 . . . . .	4034	2793
1930 . . . . .	3989	2593
1931 . . . . .	3782	2263
1932 . . . . .	3400	2005
1933 . . . . .	3516	2267
1934 . . . . .	3983	2353
1935 . . . . .	3816	2223
1936 . . . . .	4008	2418
1937 . . . . .	4668	2833
Ten-year total . . . . .	39,318	24,449

Practically all the variations of this disease have been seen except the true Riedel's tumor. The cases were classified as follows:

TABLE 2.—DISTRIBUTION OF THYROID CASES.

	Negroes.		Whites.	
	Females.	Males.	Females.	Males.
1. Diffuse toxic thyroids . . . . .	34	3	49	15
2. Diffuse non-toxic thyroids . . . . .	3	0	2	0
3. Nodular toxic thyroids . . . . .	27	3	44	5
4. Nodular non-toxic thyroids . . . . .	20	3	14	2
5. Carcinoma . . . . .	2	0	1	1
6. Suppurative thyroiditis . . . . .	1	0	0	0
Totals . . . . .	87	9	110	23
Grand totals		96		133

		Place of birth.			
		Alabama.	Georgia.	Mississippi.	Louisiana.
Negro males (9 operations)	8	8			
Negro females (87 operations)	83	72	6	4	1

Of the negro males, 6 were married and 2 were single. Of the negro females, 79 were married and 4 were single. The age incidence was interesting and according to the decades of life was as follows:

TABLE 3.—THYROID CASES ACCORDING TO SEX, COLOR AND AGE GROUPS.

	Second decade (11-20).	Third decade (21-30).	Fourth decade (31-40).	Fifth decade (41-50).	Sixth decade (51-60).	Seventh decade (61-70).
White males	1	4	2	12	3	1
White females	14	36	41	13	6	
Colored males	1	4	3	1		
Colored females	5	25	45	12		

One of the most interesting observations of these thyroid cases among negroes was their attitude toward the condition and towards the treatment, including operation. Most had postponed seeking medical aid much longer than the white patients with a similar complaint.

As observed by other workers, this favors a secondary toxic condition in a thyroid which has been "out of balance" for years. It may also account for the fact that many of the negroes have advanced toxicity with a corresponding circulatory damage when first seen. The negro's delay and apparent unconcern is detrimental because it brings him help only late in the disease. It may be that this same attitude of unconcern about his operation and other treatment is a definite aid to recovery, for he is very skeptical about everything he is told and is inclined to only believe just so much as he thinks will be to his own benefit.

The negro also has a peculiar courage when once he has accepted advice about surgical procedures; and this, together with his helpful coöperation, goes a long way towards recovery.

Among other things of interest noted in comparing the negroes and the whites following thyroidectomy was the short stay in the hospital by the majority of negro patients following operation.

It was also noticeable that their convalescence seemed easier as well as more rapid and that the negroes required very little medication such as morphine and other narcotics and sedatives.

We are of the opinion that these so-called "southern Negroes" are likely to present a different picture and different problem from their brothers, who have moved to Chicago, Detroit or any of the other larger cities of the North and East. This is, no doubt, true because the southern negro's point of view (attitude towards disease) is different from the type of negro just mentioned. After several years away from his relatives and friends, both white and black, he, in the northern metropolis, finds for himself that the body is subject to many ills, the names of which he had never heard in his southern home. For the first time he learns that he may have a gastric ulcer, or cholecystitis or even a goiter. With this change of attitude and with this increase in knowledge, he presents himself with the condition which his better informed white friend has previously experienced.

It has interested us to observe that among the diseases which many clinicians, among them Moschcowitz,<sup>3b</sup> believe due to psychogenic causes hyperthyroidism appears with equal frequency in both races. This group is held by some to consist of thyrotoxicosis, gastric and duodenal ulcer, mucous colitis, essential hypertension and cardiospasm, with other diseases bordering on the fringe of these complexes.

As to gastric ulcer in the negro race, in our experience it is rarely found and still more rarely complained of. This is confirmed by the infrequency of Roentgen ray examinations here investigating this condition. The reasons for this state of affairs, discussed elsewhere,<sup>5</sup> are in effect the same as those which govern the appearance of mucous colitis in this race. So far as that entity is concerned we can say with truth that we have yet to see the disease appear in a

negro's body in the same shape and significance as it does in our own race. If such events ever take place they have been concealed from our notice.

Cardiospasm we have never observed in a negro; we cannot recall ever having seen a negro of these parts who complained of either the subjective or objective symptoms of this disease. The name is foreign to their vocabularies.

Arterial hypertension is an actuality in the negro race and we have reason to believe that it appears more frequently in this race than in the white and that its development comes about earlier in the life of the victim. Not only are high blood pressure readings common events but death from cerebral hemorrhage and the findings of the post hemiplegic state are frequent occurrences among the negroes of the deep South. At the same time complaints due to this condition are not so frequent in the black man and woman as in their white companions. We see the elevated blood pressures, and the scars from the hemorrhage into the brains of these people but we hear far less of the vertigos, the headaches, the roaring in the ears which come to plague the lives of so many Caucasians.

Many negroes are found hard at work with blood pressures at an extremely high figure and are surprised to learn what their physician has discovered. Not only surprised but little, if any, concerned. We have seen no reason to suppose that they ever entertain any sequential ideas as to high blood pressures and a death from apoplexy. They never offer to change their way of living in any manner and resent universally the idea of refraining from hard labor on account of any such discovery. So much for these diseases as a group.

It would appear to us that in nurturing a disease (hyperthyroidism) which first became prominent in white women the negress made use of her unwonted powers of imitation. The mere appearance of a swelling of this description is such as to make an undying impression upon all who have seen it. It remains in the recollection of the onlooker after all other memory of its possessor has departed. In a way, we can say that the owners of these lesions have them on parade. They are proud of them, make the most of the opportunities to have them on exhibition and are not slow to advertise the special privileges in life to which they consider themselves entitled as a result of this achievement. This attitude has been remarked upon more than once among our cleverer writers of fiction, even if it has not as yet crept into our technical literature. The persistence with which the symptoms of this disease return again and again gives warning of the tenacity of purpose with which their possessors cling to their unusual gift.

To all the motives which underlie this as other forms of disease the negress turns a bright and curious eye. Knowing about the whites as the negro race does—our habits, personalities and inten-

tions—we may be sure that no sooner had a white woman used this disorder for making profound changes in her daily existence, than the negroes of the community became aware of the procedure. From knowledge to purpose and then to achievement are but narrow steps indeed.

The state of the knowledge of this disease in the negroes of these parts is only fair, not comprehensive. They always, so far as we have observed, call it a "goiter," and after the news has been conveyed to them of what ails them frequently inquire if it is an "inward goiter" as differentiated from an "outward goiter." We have never heard them use the word "thyroid" or "hyperthyroidism." Details of symptoms seem to be unknown to them. They have become aware that certain events follow in those who have contracted this malady. As a rule, they defer all forms of treatment until the growth is far advanced.

The results of this racial comparison in the occurrence of thyroid disease in our opinion casts doubt upon theories advanced to explain its appearance in the white race. Moschowitz<sup>2a</sup> and others have defined a type of individual in which the sickness is apt to develop. This personality possesses certain physical and intellectual stigmata; to such a degree, in fact, that the observer might be warranted in predicting when and where such a catastrophe might make its presence known. We cannot help but feel that much of what we have deduced from becoming familiar with the negro of the deep South contravenes many of these ideas. The white woman destined to fall a prey to this misfortune has been portrayed as a high strung, nervous, self centered introvert. We have no such types among the negroes who have come under our care for this form of malady. The description of such characters as met with among Caucasians display qualities physical and mental which are not encountered in the more primitive race. Aside from the exophthalmos which is so commonly found among the negroes and which is one of their racial insignia, we have searched in vain for the other well known evidences. Apart from the protruding eyes, the character of the negro as we have come to know it represents the very antithesis of that which antedates hyperthyroidism in the white. All that we have been able to ascertain informs us that in the development of this disease in the negro other circumstances play a part more important than personality characteristics.

The apparentness of the disease, whereby the sufferer presents her disability to the sight of all is a factor. While due to its passivity it may lack the drama of a major hysterical convulsion, its appeal is undeniable and more dramatic than most that we know of in the world of sickness. All that happens to such sufferers is well known to our negro companions. The benefits to the white women in curtailing their sufferings and dangers in child bearing have, we are certain, been estimated with accuracy by their negro

contemporaries. The rapidity with which imitation has progressed in this regard among negroes has exceeded that noticed in other complexes such as gastric and duodenal ulcer because the picture has been necessarily more easily understood. We have every reason to believe that the development of Graves' disease in the negro race will become more frequent as time goes on, as they are educated by their own powers of observation as to how this condition can mitigate the harshness of their lives.

**Case History and Postmortem.** CASE 97577, C.P. About 6 weeks prior to admission she first notices a throbbing parietal headache. These headaches occurred 2 or 3 times daily and lasted over 30 minutes. Definite enlargement was noticed in the anterior part of the neck 1 month before she was admitted. Dyspnea came on 2 weeks before she was seen. This symptom with its accompanying nervousness was noticed after exercise and the taking of food. Associated with the shortness of breath was a distressing pain in the left anterior chest. Her estimation of her own weight loss was 35 pounds in the previous 6 months. She had had no previous operations. The family history was negative.

*Physical examination* showed a fairly well nourished negro woman of 38 years. The examination of the head and neck was negative with the exception of a smooth, bilateral enlargement of the thyroid gland. The chest showed a slight precordial pulsation and some evidence of cardiac enlargement. The heart rate was rapid, the rhythm good. A systolic murmur was present. The blood pressure was 146/70. The abdomen and pelvis failed to reveal any disorders. Tremor was marked. Fluoroscopic examination showed a substernal mass in the upper mediastinum somewhat more marked on the right side. The BMR was +37. Laboratory examinations were negative. Lugol's solution, sedatives and bed rest were employed for 8 days when the resulting improvement made surgical interference advisable.

Under cyclopropane anesthesia a subtotal thyroidectomy was done. The microscopic diagnosis was "simple parenchymatous hyperplasia of the thyroid gland." Postoperative improvement lasted less than 24 hours, to be terminated by the patient entering a thyroid crisis accompanied by high temperature, rapid pulse and uncontrollable nervous symptoms. Despite the use of oxygen, morphine in large doses and other appropriate measures the end came 3 days after the operation.

*Autopsy Internal Examination.* Gross. Head—not opened. Thorax—both lower lobes of the lungs were dark red, solid, heavy and a little wet. They sank promptly in water. The heart and great vessels were normal. The *thymus gland* was present and much enlarged—weight 85 gm. There was about four times the normal amount of fluid in the pericardial cavity.

*Microscopic.* The air sacs in the lower lobes of the lungs are pretty well filled with leukocytes, phagocytes and desquamated epithelial cells; also there is considerable coagulated non-cellular material. The heart muscle and coronaries and aorta were normal. The thymus gland was normal microscopically.

*Diagnosis.* Marked bilateral hypostatic, catarrhal pneumonia. Moderate fatty degeneration of the liver. Moderate passive hyperemia of the mucosa and submucosa of the stomach. Much enlarged and persistent thymus. Marked serous pericardial effusion.

This is the only instance of true thyroid crisis either postoperative or preoperative that we have observed in the negro patient. There have been occurrences of this complication in the white group. In

regard to the enlarged thymus gland found at postmortem it is interesting to recall that at Mount Sinai Hospital in New York, Moschcowitz<sup>3a</sup> reports that this condition was found in 95% of all fatal cases of Graves' syndrome. He quotes Seelig<sup>4</sup> and Haberer<sup>1</sup> to the same effect. The size of the organ is known, however, to be affected by the length of time that exists between death and the onset of disease.

**Conclusions.** 1. A short series of thyroid involvements occurring in the southern negro has been described.

2. From a comparison of whites living in the same locality and at a similar time period, the disease appears to be of approximately the same frequency in the two races.

3. Why this malady should develop with such frequency in the negro, when other sicknesses believed to be of a similar origin are rare, is unknown to us.

4. We think that its accessibility to inspection, the way in which it becomes one of the easily discovered and remembered portions of the personalities which it inflicts with its presence, are factors which cannot be disregarded.

5. The observations of McCarrison<sup>2</sup> as to its increased frequency among the native population of India after the return of native soldiers from the World War points toward the potency of imitation.

6. We have never been able to lose sight of the fact that the development of this sickness offers to women a means of escape from what they esteem to be other and more pressing dangers and discomforts.

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### PSYCHIATRIC CONSULTATION SERVICE IN A MEDICAL IN-PATIENT DEPARTMENT. ITS FUNCTION IN DIAGNOSIS, TREATMENT AND TEACHING.

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IN recent years the scientific study of the interrelationship between emotional factors and bodily processes has come to occupy an increasingly prominent place in medicine. Although the importance of the rôle that personality disorder may play in physical disease has been emphasized by psychiatrists<sup>3</sup> and internists for years, many physicians continue to think of an illness as being either mental or physical. The untenability of this concept of duality between

mind and body becomes clear when attention is paid to the study of individual patients through the coöperative efforts of the internist and the psychiatrist.

Consideration of the patient as a whole tends to be lost sight of in a large urban hospital. In such a setting it has become necessary for us to investigate much that the family physician knew through social contact in the community and visits to the homes of the people whom he treated. The understanding of patients, with emphasis on relieving their pains and allaying their fears, was taught to the young assistant or medical student who served as his apprentice.

The organization of the psychiatric consultation activities in the medical in-patient service of the New York Hospital illustrates a plan which has proved practical both for the study, diagnosis and treatment of the patient and for the teaching of the house staff of the Department of Medicine and the medical student.

One full-time physician has been assigned by the Department of Psychiatry to examine and treat patients with psychiatric problems on the medical pavilions. Consultations are at the request of the physician in charge. After the psychiatrist's initial interview the patient's illness is discussed with the internist who is encouraged to carry out psychiatric treatment if this is feasible. Many patients need more detailed investigation of the physical and emotional factors, which requires further discussion between the psychiatrist and the internist. Some cases are treated by the psychiatrist on the medical service. The psychiatrist spends one afternoon a week in the Psychiatric Out-Patient Department where psychotherapy which had been started on the medical service is continued with selected patients. Other patients who need further evaluation or treatment are seen in conjunction with the internist in the medical follow-up clinic. This clinic is designed to give the medical resident staff an opportunity to study the progress of patients who have been discharged from the in-patient service.

Many patients have presented diagnostic problems to the outside physicians who have referred them to the hospital for opinion. In this group are a large number whose illness is largely a psychiatric problem. It has been found that the patient welcomes an investigation of his personality reactions and situational problems as a part of a thorough study of his condition and that he looks upon it in much the same way as he does special examinations by other consultants.

Since the opening of the present building of the New York Hospital in 1932, from 127 to 164 patients on the medical pavilions have been seen annually by a psychiatric consultant. At first, the psychiatrist usually saw the patient once and gave a single written opinion. In the last 2 years, during which time the author has acted as psychiatric consultant, the work has been expanded so as to emphasize follow-up interviews for the purpose of either further contrib-

uting to the diagnostic formulation or carrying out psychotherapeutic procedures which may be indicated. During the past year, on a medical service of 111 beds, 218 patients out of 1409 admissions (15%) have been seen by the psychiatrist. In addition there were 443 follow-up interviews, making a total of 661 visits. The consultations on the four divisions of the service were as follows: male general medical pavilion, 91 out of 425 admissions (21%); female general medical pavilion, 79 out of 391 admissions (20%); chronic infectious pavilion, 26 out of 258 admissions (10%); acute infectious pavilion, 22 out of 335 admissions (7%).

**Post-Graduate Teaching.** The purpose of the teaching is to train the interns and residents to recognize psychiatric problems, to treat those of a simple type and to delegate treatment of the more complicated cases to the psychiatrist. Stress is laid on understanding the patient as a whole and the integration of the emotional and physical features of an illness. The knowledge of psychiatry which the house officer has obtained as a medical student can be reinforced and extended by its use in dealing with patients under his care.

Instruction is carried on by means of written reports and informal discussions with attention to the psychiatric principles involved. Contact with the diagnostic problems showing prominent psychiatric features which have not been recognized by others serves as a stimulus to the development of interest and awareness of problems which will require attention, no matter what the field of specialization may be. In the setting of a medical pavilion the practical value of psychiatry and its fusion into general medical practice can be clearly seen. Teaching of this type may well supply the need which has been recognized for post-graduate psychiatric teaching. In some hospitals this has been carried out by having the intern rotate through a psychiatric service or spend a period of time in a psychiatric hospital. If there has been satisfactory instruction in the psychoses in the medical school course in psychiatry, it may be more worth while to lay emphasis on the less severe psychiatric problems seen in the general hospital and to stress the application of psychobiological principles with attention to the hereditary, constitutional, economic, social and personality features as well as the purely medical aspects. The trained psychiatrist may thus be of value in contributing to the further understanding of emotional reactions of a type that the general physician will frequently see.

**Teaching of Medical Students.** With the expansion of the teaching of psychiatry in medical schools new emphasis has been placed on instruction by use of case material found in the general hospital.<sup>1a</sup>

Teaching of the third-year students in the Cornell University Medical College is carried on through presentation of patients both on the psychiatric in-patient service and the medical in-patient service, during the trimester they are studying psychiatry. Students are divided into groups of 6. Each group sees 9 patients on the



medical service. The patient is examined by the psychiatrist before the group, important facts of the history, and physical and laboratory findings are given, and the illness is discussed with special attention to the psychodynamics and the treatment. Each student is requested to write a report on 1 patient he has seen showing psychosomatic features.

During the trimester when the students are acting as clinical clerks on the medical service, 12 weekly conferences are held at each of which a student presents a case he has worked up. He is encouraged to develop an understanding of the factors which are important in the origin of the illness, both mental and physical, and their interrelationships in the patient he has examined and with whom he has had an opportunity to develop a doctor-patient relationship. After the student has presented his findings at the conference, the psychiatrist examines the patient before the group and demonstrates significant findings in the psychiatric examination and methods of psychotherapy. The last part of the hour is devoted to an open discussion which offers the whole group an opportunity to raise questions. Informal discussions with individual clinical clerks are also held.

**Types of Problems.** The psychiatrist is consulted about a wide variety of emotional reactions which range from mild incidental personality features to major psychotic developments. Billings has reported in a study<sup>1b</sup> of 745 cases examined that the general hospital offers an excellent cross-section of psychiatric material. The patients in our study may be divided into six groups for the purpose of discussion. An analysis has been made of 218 patients seen during a single year.

The first group consists of 26 patients (12%) with minor problems of personality adjustment in which the physician feels that the opinion and advice of the psychiatrist may be of value from the mental hygiene standpoint. In the analysis of the personality features of such patients the outline devised by Diethelm<sup>2</sup> has proven useful.

This type of problem is illustrated by the case of a 14-year-old school girl who showed signs of mild emotional instability and had difficulty in cooperating with the nurses while being treated for bronchopneumonia. The patient discussed her home and school difficulties which centered around the father's having divorced the mentally ill mother, the remarriage of the father, problems in her adjustment to both the mother and the stepmother, the antagonism of an older brother, and the change from a school where there had been considerable freedom to one which had a strict set of rules. After discussions with the psychiatrist the patient showed less emotional instability. In order to help the stepmother to understand the patient, a brief formulation of the patient's situation was presented to her.

In the second group of 62 patients (28%) are primarily psychoneurotic reactions which require a study of the development of the physical and emotional symptoms and their interrelationships.

A 34-year-old, married salesman presented the chief complaints of pins and needles sensations over the left side, headache, throbbing in the neck, "irritation of the left eyeball," hot sensations over the left ear, "paralysis of the intestines," generalized "numbness," and mild depressed feelings. No constant neurologic abnormalities could be demonstrated. During the interview with the psychiatrist the patient talked of minor worries and symptoms. He then became very tense and said that what had been bothering him was the fact that 3 months before admission he had been told by a physician that he had syphilis. Symptoms had developed rapidly after that. When he was assured that no signs of syphilis had been found and that his complaints could occur because of worry he was greatly relieved and had a dramatic disappearance of all his symptoms with restoration of confidence and a normal mood reaction.

A psychoneurotic reaction of longer duration is illustrated by the following case:

A 34-year-old, single, electrical engineer had complained of fatigue and poor health since the age of 15, which had become increasingly more marked so that he had done no work for 4 years. He insisted that he had some physical illness which no doctor had been able to discover. He was told that an investigation of his personality might be of help in understanding his illness. Many emotional problems centering around his sexual drive and dissatisfaction with his work were apparent. The relationship between emotional difficulties and the increased severity of his symptoms was seen by the patient. He accepted the formulation that his illness was primarily functional and after discharge continued to have psychotherapy in the Psychiatric Out-Patient Department, with marked improvement as shown by disappearance of excessive fatigue and ability to return to work.

In a third group are 71 patients (32%) with physical illnesses complicated by psychoneurotic features. The influence of psychogenic factors is frequently prominent in such conditions as hyperthyroidism, migraine, peptic ulcer, hypertension, and asthma. Combined treatment by the internist and psychiatrist is indicated.

A 50-year-old accident prevention inspector was admitted because of persistent hiccoughing which had prevented him from taking sufficient nourishment for 6 days. Previous studies indicated that he had spasms involving the gastro-intestinal tract in reaction to emotional difficulties of many years' duration. The hiccoughs disappeared under hypnosis, enabling the internist to proceed with a further investigation of his physical condition. Roentgen-ray examination revealed a diaphragmatic hernia which it was likely he had had for many years. The surgical consultant felt that operation was not indicated. It appeared that under increased stress caused by domestic quarrels and anxiety over his work the combined influence of the emotional factors and the physical abnormality resulted in the development of the hiccoughing.

A 30-year-old milk delivery man presented symptoms of Graves' disease. He had been well adjusted until after marriage to an unstable woman who had a psychoneurotic reaction of the anxiety type. He felt insecure in his work and wished to obtain a permanent position on a police force so that he would have the assurance of a pension. While on the waiting list for

this work he developed a duodenal ulcer. This lesion responded to treatment in the hospital. On returning to work he had more difficulty in making collections from his customers and had to work overtime. Over a period of eight months he had increasing symptoms of hyperthyroidism. He was relieved by unburdening himself, developed a calmer attitude toward his life situation, responded well to the treatment preparatory to operation, and made a good adjustment to his work after thyroidectomy.

A 15-year-old high school student had had recurrent asthmatic attacks for 1 year. When seen she had had four previous admissions to the hospital in the preceding month with prompt relief of symptoms as soon as she entered the hospital. Preceding her fifth admission she was brought to the accident pavilion appearing prostrated and moaning and groaning continuously. She told the psychiatrist that she was very sensitive about her height, that she was disturbed by breaking off a friendship with a boy, and that she had considered killing herself. Asthmatic attacks had been preceded on each occasion by considerable emotional tension. After discussions she developed understanding of her illness and felt more at ease. On discharge she was referred to the Psychiatric Out-Patient Department where in further interviews she emphasized that she was excessively dependent on her mother and that she had conflict over the possible effects of masturbation and what her behavior should be while out with boys. During the year following discharge from the hospital she had several very mild spells of wheezing when situational difficulties arose but no further severe attacks of asthma.

It is important to bear in mind that, although emotional problems may be in evidence, a concomitant physical illness is the most important aspect to be considered. In many cases mild emotional disorders occur in reaction to organic change. This type of reaction is illustrated by the case of a 28-year-old married physician who was admitted complaining of excessive fatigue and muscular weakness. Previous to admission several physicians had made a diagnosis of hysteria. When seen by the psychiatrist it was evident that the patient had become depressed secondary to his physical symptoms on realization that he had a serious neurological disease—myasthenia gravis. There was marked improvement upon the administration of prostigmine. During discussions emphasis was laid on encouraging him to continue to lead as active a life as was compatible with his physical disability.

In a fourth group of 30 patients (15%) are those with findings on psychiatric examination indicating cerebral organic changes which were not severe enough to be diagnosed as a psychosis. Early changes due to arteriosclerosis, syphilis, alcohol, and pernicious anemia are included.

All patients with syphilis of the central nervous system have psychiatric examinations before and after malarial therapy in order to give diagnostic help and to aid in establishing the degree of improvement after treatment. Of the 17 patients examined, 13 showed some evidence of organic cerebral involvement. The value of psychiatric examination is illustrated by the following case:

A 45-year-old married man, 20 months before had been treated with malaria because of physical and serologic findings characteristic of general

paresis. Although he made a good superficial appearance and had no subjective complaints it was noted on detailed psychiatric examination that he showed definite memory changes, inappropriate emotional responses, a false sense of well being, and poor judgment. It was evident that organic cerebral changes on the basis of general paresis were progressing and that another course of malarial therapy was indicated.

In a fifth group are 20 patients (9%) with psychotic reactions, both functional and organic, including schizophrenia, manic-depressive psychosis, general paresis, delirium, arteriosclerotic and senile reactions, epileptic psychosis, brain tumors, and feeble-mindedness. Frequently the psychiatrist can make suggestions which may be helpful in managing such patients on the medical service. If treatment cannot be continued in the general hospital, advice may be given about arrangements for transfer to a psychiatric hospital.

A 30-year-old married automobile washer was admitted with lobar pneumonia. He developed a delirium which made it difficult to give him proper care because of his uncoöperativeness. He showed marked resentment to the fact that so many people were caring for him and made reference to suicide. Arrangements were made to have only two nurses care for him, which seemed to relieve him to a great degree. He responded some to reassurance even at times when he expressed many suspicions. When his delirium had cleared it was apparent that he had been psychoneurotic for many years. After discharge treatment of his emotional difficulties was continued in the medical follow-up clinic.

The following case illustrates the type of reaction that may require transfer to a psychiatric hospital.

A 45-year-old housewife who was going through the menopause complained of multiple physical complaints and of feeling depressed. Careful investigation failed to reveal any evidence of physical disease. Physical complaints continued. Further study showed that she was developing somatic delusions. A diagnosis of depression in the setting of the menopause was made. Since she did not improve, transfer to a psychiatric hospital became necessary.

In the sixth group are 9 patients (4%) who on psychiatric examination had no findings which could either add appreciably to the understanding of the patient or contribute positive findings to the formulation of his illness. The following case demonstrates the need for sufficient evidence in order to make a diagnosis of psychoneurosis and the significance of negative psychiatric findings.

The patient was a 45-year-old porter who complained of pain over the lower half of the back and the entire abdomen of increasing severity for two months. Studies of his physical condition failed to reveal any lesions except for an abnormal glucose tolerance curve showing consistently high blood sugar values. On psychiatric examination he showed no evidence of personality maladjustment and gave no history of emotional disturbance which might account for the development of his symptoms. He continued to have more pain, developed palpable abdominal masses, rapidly became weaker and died 3 months after being seen by the psychiatrist. The post-mortem examination showed carcinoma of the pancreas with extensive metastases.

**Summary.** The organization of the activities of a psychiatric consultation service in a medical in-patient department as described illustrates a plan which has proved to be practical. It has been found that a large percentage of the patients admitted presented problems in which coöperative investigation by the internist and psychiatrist was of definite value in diagnosis and treatment. An analysis of 218 patients, who represent 15% of the admissions during a single year to the medical pavilions, shows that 12% may be classified as having minor, incidental personality problems, 28% psychoneurotic reactions, 32% physical illness complicated by psychoneurotic features, 15% mild organic cerebral changes and 9% psychosis. In 4% there were no positive psychiatric findings which contributed to the diagnostic formulation.

Post-graduate and undergraduate teaching was carried out by individual discussions and group conferences. Stress was placed on obtaining a better understanding of the patient as a whole by considering the individual personality and its relations to somatic functions.

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## THE INITIAL NERVOUS SYNDROME OF PELLAGRA AND ASSOCIATED DEFICIENCY DISEASES\*

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It has been known for many years that pellagrins in relapse often manifest psychotic changes.<sup>6,9</sup> The association of so-called psychoneurotic symptoms with subclinical and mild pellagra is recognized less frequently and many patients with such symptoms are diagnosed as "neurasthenics."<sup>7,8</sup> Evidence accumulated from the study of over a thousand pellagrins during the past 10 years convinces

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that these symptoms have certain distinctive characteristics and that they are of significance in making an early diagnosis of the disease. Although it has been known that these symptoms improve dramatically following nicotinic acid therapy, a satisfactory study of the characteristics has not been reported since the initiation of this therapy. The present communication reports a specific study of the initial nervous symptoms in subclinical and mild pellagrins.

Sixty cases of pellagra (many of which had an associated beriberi and riboflavin deficiency) were selected for this investigation, which is restricted to an analysis of the symptoms and experiences reported by the patients. The psychiatric information obtained was gathered during repeated interviews lasting from 1 to 2 hours and by therapeutic tests in which suggestion was eliminated. Neurological studies, which will be reported separately,<sup>5</sup> were made on a number of these patients. The symptoms thus observed objectively are not all included in this report, but in certain instances are correlated with it.

The so-called psychoneurotic syndromes usually draw their contents from the life of the individual, particularly from the experiences and traumas of childhood and youth. Consequently, the basis of the neurosis may vary greatly from one person to another. We soon learned that among the pellagrins included in the present study, there was an amazing uniformity of mental symptoms which varied in intensity and had no connection with the single personality.\* These common symptoms had elementary features and followed the same pattern. They may be classified as follows:

A. THE ELEMENTARY SYNDROME:

1. Psycho-sensory disturbances.
2. Psycho-motor disturbances.
3. Emotional disturbances.

B. GENERAL SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM:

1. Weakness and increased fatigability.
2. Sleeplessness.
3. Headaches.

The first group of symptoms resembles those which may be found in disease of the basal ganglia and thalamus, while the second group represents general symptoms which usually accompany any disturbance of the central nervous system. The subsequent description demonstrates that both sleeplessness and headaches of pellagrins exhibit some special features which are uncommon and therefore are useful in making a differential diagnosis.

\* Examination of the heredity factors of 32 patients revealed: left-handedness in 19 of their families; migrainous headaches in 16 families; convulsions (different types) in 9 families; stuttering in 8 families; feeble-mindedness in 4 families; and other mental heredities in 2 families. The patients in this series were prone to have more than one of these stigmata; for instance, migrainous headaches occurred 12 times in combination with left-handedness, convulsions, stuttering or feeble-mindedness; convulsions of different types occurred 8 times, and stuttering 5 times with one of the other factors. In this small group of patients epileptoid heredity prevailed. However, the significance of this finding requires a special investigation.

A. THE ELEMENTARY SYNDROME. 1. *Psycho-sensory Disturbances.* Psycho-sensory disturbances occur in all special senses. Patients describe all outward perceptual impressions as making them feel "uneasy," or as "bothering" or "hurting" them. They dislike bright light and bright colors, and sometimes state that bright colors "run together." Noises are even more annoying than light, and sudden noises, such as the slamming of a door or the scream of a child, produce immediately an emotional shock and make the patient feel "jerky and shaky." Music of any kind makes them "uncomfortable," and many who enjoyed radio music when in good health are now forced to forego this pleasure. In the more severe cases, continual noises are almost "unbearable." Patients who paid no attention to odors prior to their illness now find odors, particularly those of the kitchen and factory, so disagreeable that they sometimes cause nausea and vomiting. Several patients stated that cooking has become "an agony." Certain strong odors, such as those of lysol, ether, or garbage, formerly considered merely unpleasant, now actually cause distress. Taste has changed to such an extent that foods formerly preferred are now disliked intensely. No rule can be established in regard to change in taste; highly seasoned food have become disagreeable to most patients, sweet foods to some, fried meats to others, and still other patients complain that some particular vegetable causes nausea. The patients can be characterized as being "on edge," irritable and tense.

Many abnormal sensations of the skin were noted. No definite differentiation could be made between those which have been considered to be subjective and those which might be caused by associated peripheral neuritis.

A prominent complaint should be stressed: patients complain of dizziness, particularly after sudden movements. Getting up, turning the head, and bending forward, immediately produce a feeling of uncertainty and difficulty in keeping balance. Patients usually have the impression of being whirled around their vertical axis, although occasionally they feel as if things are whirling around them. Simultaneously, flickering stars and dark spots appear in the direct field of vision. Sometimes the direct fixation of the eyes on an object and a strenuous stare stop the dizzy sensation. Many patients complain of dizziness while standing still and watching traffic. The majority of patients state that their weakness and dizziness is immediately increased in heavy traffic.

2. *Psycho-motor Disturbances.* In these patients the motor drive is increased. Occasionally, the attitude of the patient is quiet and they state that they are restless only on the "inside." But as a rule, they are fidgety, change their position frequently, and move around a great deal. The degree of restlessness is slight if compared with the restlessness of an apprehensive melancholic or with the excite-

ment of a severe anxiety state. Patients complain that they feel tense and have a desire to quarrel. Sometimes after quarreling their tenseness is relieved, but more frequently it is increased. They all complain that a sudden noise or a flash of light makes them jump and twitch, indicating an increased preparedness for motor action.

3. *Emotional Changes.* Emotional reactions are increased. Patients are more excitable and more sensitive than they were before their illness. Moreover, the emotional reactions are directed toward a depressive response, and a sad and gloomy mood prevails. The most striking feature of emotional feature is constant apprehension. It is not exhibited in such a demonstrative manner as in the usual neurotics, and it rarely reaches the intensity of melancholic apprehensive agitation. Many of the patients express various fears, frights and phobias, although they make a conscious attempt to suppress them. Nevertheless, this constant apprehensive mood often changes the habitual attitude of the patient. For example, a brawny coal miner said, "I'm scared to death. If I see two men fighting with their fists, it seems to me that I will pass out." Before he became ill he used to look for quarrels and liked to engage in prize fights. The emotional outlook toward the future is gloomy and pessimistic, and imminent danger is expected constantly. If patients are asked what they think when they see two cars passing each other, they invariably reply: "I expect a crash."

It is remarkable that these patients make little or no attempt to explain and to rationalize all these strange experiences. In the process of the development of psychoneurosis, somatic sensations may be compared to tools which the personality uses in order to strengthen its defenses against latent conflicts. Many neurotics are unhappy and desperate about their own unhappiness. This attitude is not characteristic of pellagrins. They describe symptoms that are strange to themselves, self-distant, and not connected with their personal life. To them these symptoms are just as elementary as aches and pains in the extremities, burning of the skin, or sensations caused by changes in the alimentary tract.

#### B. GENERAL SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM.

1. *Weakness and Increased Fatigability.* Although increased motor drive and restlessness are apparent, these patients complain of weakness. This may be due to neuritic changes and an insufficient caloric intake. However, the degree of weakness does not parallel the changes observed by Lewy, Spies and Aring<sup>5</sup> in chronaximetric examinations, and many persons whose caloric intake was adequate complained of weakness. Weakness, observed objectively, may not reach a high degree; patients are often able to do much of their work, yet they tire easily. There is a constant struggle between restlessness and the desire to rest, with restlessness often prevailing.



2. *Sleeplessness.* In many cases, sleeplessness is a major symptom. Patients usually fall asleep between 12:00 and 2:00 o'clock at night and awaken at about 5:00 in the morning. Frequently, even this short period of sleep is interrupted. Patients state emphatically that their sensory disturbances do not prevent them from falling asleep or cause them to awaken, thus further differentiating this nervous syndrome from the usual one of psychoneurosis. In spite of the constant apprehensive attitude, no bad dreams or nightmares were reported.

3. *Headaches.* Many patients report having had "sick headaches" since childhood. The headaches prior to the onset of pellagra and the headaches associated with pellagra resemble migrainous syndromes in many features. The headache usually seen in these cases occurs suddenly. It is localized in the forehead and in the temples, and is accompanied by scintillating scotomas. Nausea and vomiting are reported frequently, and sometimes relief is felt after vomiting. Many patients have dizzy spells along with the headaches. The headache syndrome exhibited by these patients is clinically indistinguishable from migraine.

Although this nervous syndrome has been found regularly in these cases of developing nutritional disturbances, the question arises as to whether these changes are produced directly by a specific deficiency of a single chemical substance. To determine the effect of certain of these nutritional substances, a few crucial studies were made. Pellagrins were given large amounts of either cocarboxylase, nicotinic acid, riboflavin, or synthetic vitamin B<sub>1</sub>. Neurologic and nervous changes were studied, and certain metabolic determinations were made on samples of blood before and after therapy. The correlated results will be published in another paper. It may be noted, however, that the intravenous injection of cocarboxylase or vitamin B<sub>1</sub> produced an immediate reversal of the neurologic signs within a few hours, while nicotinic acid, administered orally, produced a similar effect after a longer period of time. In contrast, the oral administration of riboflavin had no such effect upon the symptoms arising from the nervous system.

The following case report illustrates the effect of cocarboxylase therapy:

June 22, 1939. Mrs. F. F., a white pellagrin of 39 years complained of ill-health during the spring and summer of the past 3 years. She said that her mouth became sore, that her stomach felt "sick," and that her back and arms ached. Noises made her "jumpy and shaky," and odors "bothered" her. Sudden movements caused dizziness. She was restless, excitable, and easily frightened. She felt depressed and was apprehensive, constantly expecting some harm to befall her family. She tired easily; but although she felt tired, she kept busy all day because she was too "fidgety" to rest. She seldom fell asleep before 2:00 A.M. and usually got up at 5:30 A.M.

A total of 200 mg. of cocarboxylase\* was administered intravenously in 50 mg. doses within a period of 2 hours. One hour later she reported that she felt relaxed and stronger, that she had ceased to worry, and that she felt like resting. That night she fell asleep at 9:00 P.M. and awoke at 5:30 A.M., feeling rested. She stated that her nerves were "a whole lot better" and that she had not "felt so well in three years."

Following the administration of cocarboxylase the bisulphite-binding substances in the blood decreased. Neurologic examination showed that the severely disturbed touch and pain sensitivity which had been previously found, returned to normal within 24 hours. The corneal reflex, which had almost disappeared, improved significantly. Pupillary motor reaction and differentiation of brightness, though normal throughout this study, increased in acuteness for a period after the injections. However, abnormal tendon reflexes, nystagmus, and weakness of convergence remained unchanged after the medication.

Either cocarboxylase (or vitamin B<sub>1</sub>) or nicotinic acid may relieve the initial nervous symptoms of a developing nutritional deficiency; and both of these substances have been found to be involved in the process of oxidation of carbohydrates.<sup>2</sup> Lack of either may cause changes in the brain which, in turn, alter carbohydrate metabolism. The investigations of Himwich and Nahum<sup>3</sup> and Lennox<sup>4</sup> have shown that the brain utilizes predominantly carbohydrates. Any change in the metabolism of carbohydrates may influence the functions of the brain. In experiments on excised tissues, Dixon and Meyer<sup>1</sup> showed that the cerebral cortex and the cerebellum have the highest metabolic requirements of the brain structures. Hence, these parts should be the first to be affected by metabolic changes.

**Discussion.** It has been emphasized that no connection could be established between the experiences of the single personality and the initial nervous syndrome of pellagra. The complaints of these patients were practically identical, regardless of whether their personality was simple or complicated, or whether they were illiterate or educated. Clinical observation revealed no causal relationship of the symptoms to environmental stresses and strains, to personal conflicts, or to any of the other usual underlying causative factors of neurosis. It appears, therefore, that this nervous syndrome may indicate a disturbance of the central nervous system. Large doses of vitamin B<sub>1</sub> or nicotinic acid relieved the symptoms rapidly.

The symptoms of the initial psychiatric syndrome of pellagra are definite. They are especially important to the physician treating the subclinical cases in which the signs of pellagra are inconclusive. Since nutritional deficiencies may be related to neurotic

\* Furnished through the courtesy of Merek & Co., Rahway, N. J.

manifestations, examination for the nervous symptoms of such deficiencies should become a matter of routine psychiatric examination. Administration of large amounts of either nicotinic acid or thiamin, under controlled conditions, will aid in establishing the correctness of the diagnosis.

Attention may be called to another important aspect of the problem. It has been shown by this study that developing pellagra often causes a rapid breakdown of personality. Men previously strong, courageous, and enduring, become shaky, weary, and apprehensive even before the usually recognized clinical signs of pellagra develop. Nutritional deficiencies widespread in a population may not only weaken the strength, but may also break down the morale. Subclinical pellagra or beriberi may be an important factor in the fighting morale of an army, supporting Napoleon's contention that "an army marches on its stomach."

**Conclusions.** 1. Sixty patients with subclinical and mild pellagra and associated deficiencies were examined and special attention given to their subjective symptoms. The symptoms were found to be uniform, and they had no connection with the personality.

2. The symptoms of the initial nervous syndrome associated with pellagra are: *a*, hyperesthesia to all forms of sensation; *b*, increased psycho-motor drive; *c*, increased emotional drive with a definite trend toward depression and apprehension; *d*, weariness and increased fatigability; *e*, headaches; and *f*, sleeplessness. In general, these patients appear to have anxiety states with depressive features.

3. The etiology of this syndrome was established by the administration, under controlled conditions, of large amounts of nicotinic acid, cocarboxylase, or vitamin B<sub>1</sub>. Following the administration of these substances, the symptoms diminished rapidly in intensity or disappeared entirely. Despite the clear-cut manner in which these substances are specific, the usual case, in addition, should have a well-balanced diet. Riboflavin and vitamin B<sub>6</sub>, however, did not produce the same effect.

4. Nutritional deficiencies may be involved etiologically in psychiatric disturbances.

5. This investigation indicates that nutritional deficiencies may cause a disintegration of the personality, including a breakdown of morale.

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## THE ABSENCE OF REACTIONS FOLLOWING THERAPEUTIC DOSES OF NICOTINIC ACID AMIDE.

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NICOTINIC acid, first used by Elvehjem, Madden, Strong and Wooley<sup>4</sup> to cure black tongue or canine pellagra, has been amply demonstrated to have remarkable curative value in human pellagra.<sup>5,9,13</sup> This is so, despite the fact that pellagra is a syndrome due to multiple deficiencies and that patients who are deficient in one factor of the vitamin B complex may be expected to be deficient in and need supplements of other factors to produce a complete cure.<sup>6,10,11,15</sup>

Free nicotinic acid has not been found in animal tissues. It is not the complete vitamin. Elvehjem and his associates<sup>4</sup> isolated nicotinic acid amide from liver extract. Nicotinic acid is a necessary building stone with which the organism can synthesize complex molecular structures, which act as enzymes, essential for normal cellular metabolism.<sup>3,17</sup> Consequently, it is not surprising that nicotinic acid should have pharmacological effects of its own, if it is absorbed more rapidly than the organisms can synthesize it into the natural vitamin. These effects have been reported by others.<sup>8,12,14</sup> Unless large doses of nicotinic acid are given, unpleasant symptoms are limited to a peripheral vasodilatation with increase in skin temperature and sensations of burning, itching or tingling which is usually most pronounced in the face and ears. This need not be serious, because it does not usually occur after moderate doses until the patient has received nearly the therapeutic amount of the drug.

Nicotinic acid amide has been reported by several workers to be effective in the treatment of human pellagra.<sup>1,2,7,13</sup> Because nicotinic acid amide is a substance occurring naturally in the body, it seemed likely that it would not produce reactions like those produced by nicotinic acid. Vilter, Bean and Spies<sup>16</sup> reported that the intravenous injection of "much larger" doses of nicotinic acid amide did not produce flushing reactions. Alport, Ghalioungui and Hama<sup>1</sup> reported that 1 gm. doses of nicotinic acid amide led only to transient headache in 2 cases; it was not stated when in the course of treatment these large doses were given.

Our experience confirms that of Spies, Bean and Stone<sup>12</sup> and others that reactions to nicotinic acid are less frequent and less intense in pellagrins than in normal individuals. Among a large number of patients treated, most of whom would be classed as chronic or "subclinical" pellagra, we have seen only 4 who had mild flushing

following one of the early 60 mg. doses and these reactions did not recur consistently until after a good number of further doses. Consequently it seemed desirable to test further the tolerance for nicotinic acid amide.

**Method.** Seventeen patients were given nicotinic acid until they consistently had flushing reactions following 40 mg. doses, given in tablets by mouth after meals. The first 5 patients were then given nicotinic acid amide in tablets by mouth, before meals.\* The initial dose was 100 mg. Each subsequent dose was increased by 100 mg. until these patients took doses of 300, 300, 400, 500 and 500 mg., respectively. One patient took 1.2 gm. in 3 consecutive doses of 300, 400 and 500 mg. within 10 hours.

Skin temperature determinations were not made because the peripheral vasodilatation which is produced by nicotinic acid is readily apparent. No cutaneous flushing was observed in, and no abnormal cutaneous sensations were reported by, any of these patients. No abdominal or cerebral symptoms such as may follow large doses of nicotinic acid were reported. No significant change in pulse rate or blood pressure was observed. There was no change in the electrocardiograms of 2 subjects following the ingestion of 500 mg. of nicotinic acid amide. There was a slight decrease in amplitude of the *T* wave in Lead II in one subject who subsequently was given 750 mg. of the drug by mouth.

Such large doses would rarely be indicated. Consequently, in subsequent observations, 12 patients who had been saturated with nicotinic acid as described for the first subjects were given single doses of 250 mg. of nicotinic acid amide, by mouth, before meals. In no instance has there been any evidence of a toxic effect.

**Summary.** Doses of nicotinic acid amide up to 500 mg. by mouth, while fasting, have been given to patients who had previously been saturated with nicotinic acid so that they consistently had flushing reactions following 40 mg. doses, orally, after meals. Ingestion of these doses of the amide was not followed by peripheral vasodilatation or any other of the symptoms which follow the ingestion of large doses of nicotinic acid.

\* Nicotinic acid was furnished by the Upjohn Company; nicotinic acid amide was furnished by General Biochemicals, Inc.

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## BOOK REVIEWS AND NOTICES

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**PROCTOSCOPIC EXAMINATION AND DIAGNOSIS AND TREATMENT OF DIARRHEAS.** By M. H. STREICHER, M.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medical Research and Educational Hospital, and Department of Surgery, Grant Hospital of Chicago. Pp. 149; 39 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$3.00.

THIS is a very simply written little book which discusses briefly the instruments that are used for proctoscopic and sigmoidoscopic examinations and the technique used in the passing of the instruments. The story is related so briefly that one gets the impression that there is really very little skill necessary in doing a good examination. Some very interesting illustrative cases are given in Chapter IV, but far too few for the neophyte to obtain more than a very superficial knowledge. Part II, which discusses the diarrheas, is also brief but well done. There is a satisfactory bibliography. The volume would be more widely read were the price not so high for the amount of material it contains. I. R.

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**RECENT ADVANCES IN MEDICAL SCIENCE. A Study of Their Social and Economic Implications.** By SIR EDWARD MELLANBY, K.C.B., M.D., F.R.C.P., F.R.S., K.H.P., Secretary to the Medical Research Council. (The Rede Lecture delivered before the University of Cambridge on April 28, 1939.) Pp. 62. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, 75c.

IN this small volume the author discusses the significance of medical science as related to society as a whole. It is enlightening, interesting and convincing. If we agree with him that human life and health, developed and enjoyed to a maximum degree by each individual, are themselves the most precious of all things in the world, then medical science may be regarded as the most concrete factor in advancing civilization. The author traces back to medical science some of the most desirable characteristics of modern society, such as cleanliness, but he also points out that there is an unreasonable lag in the time between the disclosing of new medical knowledge and its application for the benefit of society as a whole.

The relation of medical science to medical practice and to public health, the influence of medical science on health, fertility and population, and its necessary rôle in making tropical countries habitable for those who can do most in their development, are among the topics discussed in this lecture. It is distinctly encouraging to read a summary of the effects of the advances in medical science, and the possibilities that are indicated for the future are stimulating. The lecture closes with this statement: "There is no limit to the amount of knowledge to be gained, if the medical scientist is given the opportunities and facilities for his work. Would that the same could be said about the wisdom necessary to make the best use of this knowledge."

This brief résumé of the significance of medical science should be read by students of medicine, by those engaged in medical research and by anyone interested in general problems of health, as a means of orientating themselves more fully in the larger needs of modern society. G. R.

THE ELECTROCARDIOGRAM AND X-RAY CONFIGURATION OF THE HEART. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P., Associate in Medicine, and Chief, Cardiographic Laboratory, the Mt. Sinai Hospital, New York; Associate in Medicine, The College of Physicians and Surgeons, Columbia University, New York. Pp. 222; 71 cases with 204 engravings. Philadelphia: Lea & Febiger, 1939. Price, \$6.50.

THIS is a concise atlas emphasizing the correlation to be found between the size, shape and position of the heart and the electrocardiographic pattern. The numerous plates are clearly reproduced, with teleroentgenograms and electrocardiograms placed adjacently. The legends and the bibliography are adequate. A few of the electrocardiographic patterns attributed to alterations in the electrical axis might also be interpreted as being due to myocardial damage. The book is to be recommended as a most useful source for reference, either for the beginner, or for one interested in enlarging his knowledge concerning the author's timely point of view.

W. J.

NITROUS OXIDE-OXYGEN ANESTHESIA. McKesson-Clement Viewpoint and Technique. By F. W. CLEMENT, M.D., Director of Anesthesia at Flower Hospital, The State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent Hospitals, Toledo, etc. Pp. 274; 70 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$4.00.

THE author has combined his ideas on nitrous oxide with those held by the late E. I. McKesson. General topics such as preoperative sedation, respiration, anoxemia, shock, and others are considered. The most extensive uses ever made of nitrous oxide are described in some detail, but the author has not reckoned with the limitations in skill of the average anesthetist with this anesthetic. The anesthetic techniques in common use with inhalation anesthesia, also special methods, are described in connection with nitrous oxide, cyclopropane and ether. The book is a contribution to anesthesia; however, it can only be recommended with some reservation in light of the recent knowledge of insidious damage from oxygen shortage to various body tissues. Anesthetists should find the book practically useful as well as a memorial to Dr. McKesson.

I. T.

HARVEY CUSHING'S SEVENTIETH BIRTHDAY PARTY, APRIL 8, 1939. Speeches, Letters, and Tributes. Pp. 146; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1939, for The Harvey Cushing Society. Price, \$3.00.

SIX months before Dr. Cushing's death almost to a day, the Harvey Cushing Society celebrated with him his seventieth birthday. In order to allow his many admirers who were not able to be present "to share with the Society and its guests a little of the warmth and gay intimacy of the occasion," this small volume of speeches, letters and tributes has been prepared. It is a welcome companion to the Cushing Bibliography.

E. K.

PHYSIOLOGICAL DIFFERENTIATION IN *Lymnæa Columella*. By JOSHUA L. BAILY, JR. With a Foreword by RAYMOND PEARL. (The American Journal of Hygiene, Monographic Series, No. 14, April, 1939.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 133; illustrated. Baltimore: The Johns Hopkins University Press, 1939. Price, \$1.00.

THIS very adequate biometric treatment of painstaking series of observations proves that the offspring from two populations of a pond-snail, collected somewhat over 100 miles apart but raised under identical laboratory

conditions, showed very significant differences between statistical means, obtained from physiologic characteristics of longevity, fecundity and growth. One of the populations seemed to constitute a more settled and stable stock, with less acute infant mortality and less variability with respect to longevity and fecundity although not in regard to growth. However, the Reviewer suspects that equally accurate measurements of morphologic structures might disclose similar divergences between the means of the two stocks, even though inspection did give valid evidence of their close intergradation in shell-form.

H. B.

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THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 11, Scarlet Fever to Testis, Undescended; Vol. 12, Tetanus to Yellow Fever. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., JAMES YOUNG, M.D., F.R.C.S. Ed., SIR LEONARD ROGERS, M.D., LL.D., F.R.C.P., and F. M. R. WALSH, M.D., D.Sc., F.R.C.P. Pp. 730; 93 illustrations and 17 plates (6 in color) (Vol. 11); Pp. 726, 48 illustrations, 12 plates (3 in color) (Vol. 12). London: Butterworth & Co. (Publishers), Ltd., 1939. Price, \$12.00 per volume.

Among the more important articles in Vol. 11 are those on Sex Hormones, Occupational Diseases, Skin Tumors, Spinal Cord Diseases, and Syphilis (this approaches monographic proportions).

More than one-fifth of Vol. 12 is devoted to the toxicology of criminal, accidental and industrial poisonings, and the subject is further augmented by many cross-references. This is a well-considered, useful up-to-date presentation of a subject none too well represented in English medical literature. Of the other longer articles, one notes that more space is given to typhus fever than to tuberculosis; more to yaws than to yellow fever. Disorders of the Uterus is given 78 pages; Tumours only 11. The 35 pages on Vitamins are useful. Though some of the latest developments, such those of vitamin K, are missed, the difficulty in keeping abreast with this rapidly moving subject is appreciated by the Reviewer. In fact, these volumes can be warmly recommended, for the reasons already given in notices of earlier volumes.

E. K.

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MALARIA IN PANAMA. (The American Journal of Hygiene, Monographic Series, No. 13, January, 1939.) Supported by the De Lamar Fund of The Johns Hopkins University. By JAMES STEVENS SIMMONS, B.S., M.D., Ph.D., S.D., Lieutenant Colonel, Medical Corps, U. S. Army; President, Army Medical Research Board, Ancon, C. Z., 1934-5. With the Collaboration of GEORGE R. CALLENDER, M.D., Lieutenant Colonel, Medical Corps, U. S. Army, etc., DALFERES P. CURRY, M.D., Major, Medical Reserve Corps, U. S. Army, etc., SEYMOUR C. SCHWARTZ, B.S., M.D., Dr.P.H., Lieutenant Colonel, Medical Corps, U. S. Army, etc., and RAYMOND RANDALL, D.V.M., Lieutenant Colonel, Veterinary Corps, U. S. Army, etc. Pp. 326; 32 figures and 58 tables. Baltimore: The Johns Hopkins Press, 1939. Price, \$1.10.

In spite of adequate understanding of the nature of malaria and well-developed control practices and clinical management, this disease still remains the great obstacle to development of tropical lands. The Canal Zone of Panama is one region in the tropics where neither funds nor personnel have been stinted in the effort to be rid of malaria. Yet certain problems are still to be solved. The authors of this account have done a valu-



able service in gathering and analyzing the great amount of material that is available. The book is divided into three sections: Part I, "Malaria on the Isthmus of Panama (1501-1938)" is made up of two chapters and notes on the history of malaria on the isthmus of Panama, and the present distribution of malaria in the Republic of Panama. Part II, "Malaria in the Panama Canal Zone (1904-1938)" contains five chapters in which are discussed the Canal Zone, malaria among Panama Canal employees, human carriers of malaria in the Canal Zone, the anopheline mosquitoes of the Canal Zone, and sanitary methods used for the control of malaria in the Canal Zone. Part III is an account of malaria in the military forces of the Canal Zone (1911-1938) separated into four chapters. A brief résumé, a bibliography and index complete the book. H. R.

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**SUPERFLUOUS HAIR AND ITS REMOVAL.** By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by M. H. MARTON, M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, \$2.00.

In this small volume the author summarizes briefly existing knowledge regarding a problem of considerable importance to the individual suffering from an unusual growth of hair. He discusses briefly the question of anatomy, the methods of hair removal employed in various parts of the world, and the various techniques that are used. This is followed by chapters dealing with the removal of hair as it is carried out in the various parts of the body by experts, and a final chapter deals with its removal by the patient herself. Numerous prescriptions for depilatories are included. The volume would seem to have a very definite value in the library of the dermatologist and cosmetician, but in the hands of the layman might easily lead to undesirable complications. D. M.

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**CARDIOVASCULAR DISEASES. Their Diagnosis and Treatment.** By DAVID SCHERF, M.D., and LINN J. BOYD, M.D., F.A.C.P., Associate Professor of Clinical Medicine and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals. Pp. 458; 10 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$6.25.

This is a very readable adaptation of Dr. Scherf's *Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen* (Vienna, Julius Springer, 1938). It contains well-indexed dissertations on all of the important aspects of cardiovascular disease. Emphasis is placed upon physical diagnosis, abnormal physiology, and principles of treatment. For the physician desiring to enlarge his knowledge in this field, the book will supply much of practical value. There are many concepts and recommendations of continental flavor, all of which the critical American reader will not be able to accept. W. J.

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**ARCHITECTURE OF THE KIDNEY IN CHRONIC BRIGHT'S DISEASE.** By JEAN OLIVER, Professor of Pathology, Long Island College of Medicine; Pathologist, The Hoagland Laboratory; Formerly Professor of Pathology, Stanford University. Pp. 195; 59 text illustrations (some in colors); 23 plates; 16 stereograms. New York: Paul B. Hoeber, Inc., 1939. Price, \$10.00.

This book is a significant contribution to studies in the pathology of Bright's disease, a tribute to painstaking research and a challenge to further investigation along these lines. The author's premise, that the necessity of basing a three-dimensional histopathologic concept on deduction from a two-dimensional picture may lead to grave error in the true visualization

of the diseased kidney, seems to be a logical one. By means of microdissection and plastic reconstruction techniques the author has studied a number of diseased kidneys, comparing his own morphologic findings with the flat histologic sections of the same tissues and the clinical course of the patient. These studies are copiously illustrated with drawings and photographs. The author also reexamines various theories regarding the altered morphology of the diseased kidney in its relation to altered function and finds certain of them lacking in the light of his own investigations.

Certainly the morbid anatomic basis of Bright's disease is a shifting one. These investigations and further investigation with the three-dimensional concept as a background will do much to fix the pathologic basis firmly, which in turn will aid greatly in solving the vital problem of accurate correlation between the clinical manifestations and altered morphology in Bright's disease.

F. M.

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**PROTOZOÖLOGY.** By RICHARD ROKSABRO KUDO, D.Sc., Associate Professor of Zoölogy, The University of Illinois. Enlarged and completely rewritten edition of Handbook of Protozoölogy. Pp. 689; 291 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1939. Price, \$6.50.

In preparing a second edition of his "Handbook of Protozoölogy," the author has not only revised, but has rewritten and greatly expanded the text, and has therefore given it a new title. There are many new and up-to-date illustrations and many of the former figures have been redrawn, regrouped and enlarged. Much new material has been added to the introductory section which now includes chapters with the headings: 1, Introduction, 2, Ecology, 3, Morphology, 4, Physiology, 5, Reproduction, 6, Variation and Heredity. A total of 170 pages is devoted to this series of chapters in contrast to the 59 pages of introductory material of the earlier edition.

The taxonomic part of the book, which covered 360 pages in the previous edition, has been expanded to 471 pages. The taxonomy has been modernized throughout, but more especially in the parts dealing with the Mastigophora, Sporozoa and Ciliata. In the new edition, 1075 genera and 1530 species are characterized in comparison with 686 genera and 915 species in the "Handbook." The appendix of the first edition has been omitted, but the index, which filled 30 pages in the earlier edition, has been expanded to 46 pages in the new. Altogether, this rewritten, enlarged and modernized "Protozoölogy" is a distinct advance over the earlier "Handbook of Protozoölogy" by the same author.

D. W.

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**PERSPECTIVES IN BIOCHEMISTRY.** Thirty-one Essays Presented to Sir Frederick Gowland Hopkins by Past and Present Members of His Laboratory. Edited by JOSEPH NEEDHAM and DAVID E. GREEN. Pp. 361; illustrated. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, \$4.75.

THIS is the third reprinting of these essays which were originally published in 1937 and presented to Sir Frederick Gowland Hopkins on the 75th anniversary of his birth. In the editors' introduction they state, "The aim of the writers of the following essays has been to indicate the most promising lines of advance in the various fields which they survey, and while maintaining a due standard of criticism, to speculate a little on the likely paths of future thought and discovery." The essays cover a very wide range of physiology taken in its broadest sense. They are very clearly written and in a sufficiently non-technical manner that anyone at all familiar with the physiological sciences can profit by them.

J. J.

**INFECTIONS OF THE HAND.** By LIONEL R. FIFIELD, F.R.C.S. ENG., Late Surgical Registrar and First Assistant and Demonstrator of Anatomy, London Hospital; Demonstrator of Minor Surgery, London Hospital. Second Edition by PATRICK CLARKSON, F.R.C.S. ENG., Surgical Tutor, Guy's Hospital; Demonstrator of Anatomy and of Operative Surgery, Guy's Hospital Medical School. Pp. 167; 57 illustrations, including 8 plates (2 colored). Second Edition. New York: Paul B. Hoeber, Inc., 1939. Price, \$3.25.

In the preface to the first edition of this book Mr. Fifield acknowledged his indebtedness to Kanavel and justified the publication of this work on the ground of the need for a "much smaller and simpler book for students, house-surgeons and practitioners." The second edition, which was completely rewritten and enlarged by Mr. Clarkson after the author's untimely death, can perhaps be similarly justified, though the Reviewer would hesitate to recommend the use of this book, rather than that of Kanavel, to any one interested in infections of the hand. It would seem that it would be possible for any one, student or practitioner, to find easily any information he desired in the larger monograph.

This is undoubtedly an excellent little volume, however, well illustrated and written, and for those who desire a small handbook this one can be recommended. I. R.

**STERILITY AND IMPAIRED FERTILITY.** Pathogenesis, Diagnosis, and Treatment. By CEDRIC LANE-ROBERTS, M.S., F.R.C.S., F.R.C.O.G., Gynecological Surgeon, Royal Northern Hospital; Consulting Obstetric Surgeon, Queen Charlotte's Hospital; ALBERT SHARMAN, M.D., M.R.C.O.G., Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, KENNETH WALKER, F.R.C.S., Surgeon to the Genito-Urinary Department, Royal Northern Hospital, and to St. Paul's Hospital; and B. P. WIESNER, D.Sc., Ph.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital. With a Foreword by THE RT. HON. LORD HORDER, G.C.V.O., M.D., F.R.C.P. Pp. 419; 87 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$5.50.

IN contradistinction to the usual book on sterility by a single author, the volume in review has been written by a group of two gynecologists, a urologist, and a biologist. The latter is particularly noted for his work on endocrinology. This group presentation of the subject makes for a well rounded out consideration of all aspects of sterility and impaired fertility. In a foreword, Lord Horder states that the three great advances in the subject of childless marriages in recent years, are rescarches into spermatogenesis and the morphology of spermatozoa, a great increase in our knowledge of the sex hormones and the introduction of new techniques in the investigation of tubal patency.

The book opens with a general survey of the problem, its terminology, incidence and general biologic factors concerned and the task of the physician who handles such cases. The authors introduce a new classification, dyskyesis, with a discussion of its significance. The influence of contraception on childless marriages is discussed and the eugenic factor is well handled.

The first five chapters of the book take up a discussion of the male factor in the childless marriage, with particular reference to the examination of the husband and his sexual history. A chapter on the constitution of the semen, one of the longest chapters in the book, brings out the biologic consideration of the spermatozoa, a discussion of the normal and abnormal types and the various factors influencing spermatogenesis. The great variability of head length, in their opinion, signifies abnormal spermatozoa.

They state that even grossly abnormal spermatozoa may exhibit normal motility and the capacity for propulsion is therefore, not a reliable index for normality.

The chapter on the Assay of Male Fertility makes practical use of the analysis and examination of the semen. The authors do not share the view of Randall and Wilson that inflammation of the prostate and seminal vesicles constitutes a very common cause of sterility.

The text proceeds further into a description of the male reproductive mechanism and its disturbances and the investigation of such disturbances. The authors state a preference for the technique of testicular biopsy used in the Squier Clinic. They regard acute orchitis of mumps and chronic orchitis of syphilis, as the two most important diseases of the testis with reference to sterility. In this section, as well as in a later chapter on the treatment of female sterility, there is a long discussion on the dietary disorders and dietary adjustments and a considerable discussion of vitamin E deficiency. They regard degeneration of the seminiferous epithelium caused by E-deficiency as irreversible. They regard vitamin E therapy as one of prevention rather than one of cure. Since no method of assessing vitamin E has been established they suggest the equivalent of  $2\frac{1}{2}$  to 5 gm. Wheat Germ Oil daily, or its concentrate equivalent. Various urologic operations are discussed in detail, as well as the use of hormones.

Whereas the male assay is positive in the inspection of the gametes, no similar procedure is possible in the female, and the authors discuss and describe the various measures to be used in the clinical and gynecologic examination of the infertile female partner. Modern physiology is detailed, recognition of the anovulatory cycle is discussed, and the diagnosis of physiologic, functional and pathologic causes are also thoroughly detailed.

There is an unusually elaborate discussion of the relationship of hormones to sterility and their use in infertile males and females. A series of appendices complete the book. These comprise case histories and technical details of practically all tests mentioned which are not otherwise discussed in the text. A well considered bibliography is appended.

This is one of the most thorough treatises on sterility and impaired fertility which has come to our notice. The group handling of the subject makes for completeness of discussion. The volume is highly recommended not only to the general practitioner or obstetrician, to whom childless women first come, but as well to the urologist who more and more frequently is being consulted, and to the biologist whose assistance is necessary in solving the finer points of the endocrine aspects of the problem.

P. W.

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AN INTRODUCTION TO MEDICAL MYCOLOGY. By GEORGE M. LEWIS, M.D., Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University; Instructor in Medicine (Dermatology), Cornell University, etc., and MARY E. HOPPER, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 315; 71 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, \$5.50.

This is a volume which has been long and eagerly awaited by dermatologists. The subject matter is arranged primarily from the clinical angle, but there are shorter chapters on such phases as history, classification, structure and physiology, which give at least a smattering of the biology of fungi. A more lengthy chapter deals with the characteristics of pathogenic fungi which is entirely adequate to give the clinician an insight into the etiology of the mycoses that he handles. In line with the general policy to make the book useful in practice, particular emphasis has been placed on immunity and cutaneous sensitization. The body of the book is taken

up with the systematic discussion of first the superficial and then the deep mycoses. The bibliography is rich and up to date.

Laboratory methods are covered in a way that has not been accomplished in any book to date. Such phrases as the collection of materials, selection of instruments and glassware, the direct microscopic examination, the appearance of fungus in diseased material and even saprophytes and artefacts are discussed. Cultural methods and features, both gross and microscopic, occupy several short chapters. The use of Wood's light and the performance of the trichophytin test have not been neglected. In short, the subject of cutaneous mycoses has been completely covered, with special emphasis on the clinical aspects but without neglecting the laboratory ones.

The book is beautifully printed in large type and on enamel stock throughout. The illustrations are superlative. Although there are only 71 figures, many of them are broken up into perhaps a dozen smaller ones which are nevertheless so compactly arranged that the essential message is adequately conveyed. The authors have been remarkably successful in thus condensing a rich message in a remarkably small number of square inches of halftones. This applies to the illustrations both of clinical conditions and laboratory subjects. In short, the book is a model of completeness, accuracy, efficiency and artistry which no dermatologist can afford to do without. F. W.

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**PRIMER OF ALLERGY.** A Guidebook for Those Who Must Find Their Way Through the Mazes of This Strange and Tantalizing State. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 140; illustrated (by John P. Tillery). St. Louis: The C. V. Mosby Company, 1939. Price, \$1.50.

AFTER writing two editions of a book on allergy intended both for physicians and patients, the author has now written separate volumes for each, to the immeasurable advantage of both. This handy little volume, in addition to an adequate and lucid presentation of theoretical matters, contains a wealth of practical advice for allergies, amusingly written and illustrated. Physicians should recommend it to their allergic patients as an invaluable *vademecum*. R. K.

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**PROCTOLOGY FOR THE GENERAL PRACTITIONER.** By FREDERICK C. SMITH, M.D., M.Sc. (Med.), F.A.P.S., Proctologist to St. Luke's and Children's Hospital, Philadelphia; formerly Associate in Proctology, Graduate School of Medicine, University of Pennsylvania. Pp. 386, 141 illustrations and 3 color plates. Philadelphia: F. A. Davis Company, 1939. Price, \$4.50.

THIS book, planned to give the general practitioner the essentials of proctology, was written by a man who has had considerable experience in the proctologic surgery. It is essentially a compilation of facts from various works on the same subject, to which the author has added notes from his own experience. The illustrations are only fairly good and approximately two-thirds of them are reprints from other works on proctology. The first few chapters are given to anatomy and malformations of the rectum and anus, followed by chapters on diagnosis, treatment and anesthesia. The sections on the usual diseases of the perianal region and anal canal contain little that is new. The author still subscribes to the old idea that strangulated internal hemorrhoids should be treated conservatively. He includes a chapter on parasites of the lower bowel and one on diets. Throughout the book are numerous prescriptions, some of which are used by the author and others which have been culled from the literature. This book may serve its intended purpose of giving the general practitioner the essential facts of proctology. It does not, however, compare favorably with numerous recent texts on the same subject. L. F.

**DISEASES OF THE MOUTH AND THEIR TREATMENT.** A Text-book for Practitioners and Students of Medicine and Dentistry. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., DR. MED. DENT., Professor Emeritus of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, Philadelphia, and SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Professor of Clinical Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania; Visiting Dermatologist, Mt. Sinai Hospital, Philadelphia General Hospital, Home of St. Michael's, and Eaglesville Sanatorium, etc. Pp. 670; 324 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$9.00.

It is commendable that a second edition should become necessary in a comparatively short time. New subjects have been added, namely lymphadenitis, Paget's disease, Schüller-Christian's disease, hereditary pseudo-hemophilia, sarcoidosis and others. The text continues to be uniformly good and the format and printing excellent. Most of the illustrations in color are poor (Plate 3, facing p. 210, is indeed grotesque) and mar an otherwise highly presentable volume. F. W.

**OBSTETRICAL PRACTICE.** By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 858; 1043 illustrations. Second edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$7.00.

THIS excellent textbook on the practice of obstetrics has been expanded by 155 pages of text in its second edition. Evidence of a comprehensive review of the literature appears particularly in the "Chapter on the Toxemias of Pregnancy" and in the three-fold increase in references included in the bibliography. A noteworthy and very timely expansion of the text regarding nutrition occurs in the subject matter of the "Management of Pregnancy." In spite of the addition of so much new material, the author has succeeded in retaining a personal note throughout. While the chapter on "Resuscitation of the Newborn Child" has been brought up to date, there is still lacking from the book a chapter on "Obstetric Injuries of the Newborn" and "The Diseases of Early Life," which might well be in place in a book of this character. Again the book is most warmly recommended as an outstanding text. P. W.

**A SYNOPSIS OF REGIONAL ANATOMY.** By T. B. JOHNSTON, M.D., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 462, 17 illustrations. Fourth edition. Philadelphia: Lea & Febiger, 1939. Price, \$4.50.

THIS book was prepared by the author as an aid to his students in dissection. A very concise text, it is almost without illustrations because the author believes the student should refer to dissected parts rather than to illustrations in a dissecting manual for his information. He emphasizes that the book should not be consulted at all until the actual work of dissection has been completed. The only illustrations are diagrams of the nerve tracts of the spinal cord, brain stem and brain. The text follows in anatomical order as the dissection is carried out by the student. Each anatomical part is described, the important sections being emphasized with italics. There is little or no effort to make any practical application of the anatomy described. In the new edition a considerable revision of the material on the central nervous system has been added. The book is well printed. It should prove a considerable help as a handbook for students in dissections of anatomy. L. F.

**PSYCHOBIOLOGY AND PSYCHIATRY.** A Textbook of Normal and Abnormal Behavior. By WENDELL MUNCIE, M.D., Associate Professor of Psychiatry, Johns Hopkins University; Associate Psychiatrist, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital. With a Foreword by ADOLPH MEYER, M.D., LL.D., Sc.D., Henry Phipps Professor of Psychiatry and Director of the Department of Psychiatry, Johns Hopkins University. Pp. 739; 69 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, \$8.00.

It is said, "Psychobiology then is the study of those functions distinctively human, the things that man is best known for, the mentally integrated performances." In this psychiatric presentation of Adolph Meyer's psychobiologic concepts, frequent use is made of his novel, cartridge-shaped designs for life charts, where in the longitudinal dimension is shown the development and course of a disorder, while in cross section, such manifestations as may appear more suddenly, are depicted. With full clinical data plotted in this way, one unfamiliar with the system would need an interpreter.

The text is divided into four parts: Part I. Psychobiology—The Study of Normal Behavior. Historical and philosophical bases of psychobiology; student's personality study. Part II. Abnormal Behavior—Pathology and Psychiatry. Historical account; examination methods and immediate findings; detailed study of main reaction types (pathergasias); major reactions (holergasias); thymergic reactions: elations; topical delusional states and para-reactions: parergasia; the support disorders (dysergasia); the acquired organic deficit reactions (anergasia). Part III. Treatment. General bases of treatment and procedure; important therapeutic aids; treatment of the major reactions (holergasias); para-reactions; dysergasic reactions; organic deficit states. Part IV. Historical Survey in Bibliography of the Development of the Concepts Underlying the Principal Reaction Sets (except the organic deficit states). Neurasthenia; hypochondriasis; anxiety states; obsessive-compulsive-ruminative-tension states; hysteria; manic-depressive psychoses; paranoia and paranoid conditions; parergasia; dysergasia. Part III, treatment, is mostly generalities; and in Part IV, two-thirds of the space is lost through blank, parallel columns. The term, *dementia praecox*, has most yielded to schizophrenia, and psychobiologists now wish it called, parergasia. One doubts if these new names for old diseases shall find general acceptance. The work is primarily for students but the more formal psychiatric books seem better adapted to their needs, perhaps with collateral excursions into psychobiologic psychiatry. Adolph Meyer is tireless, and the most original worker in the American school of psychiatry; but his somewhat nubulous presentations have not found great support beyond his devoted assistants. He does not appear to complete his works—perhaps the trait of a genius, as with Leonardo da Vinci. N. Y.

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**OFFICE GYNECOLOGY.** By J. P. GREENHILL, B.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago; Professor of Gynecology, Cook County Graduate School of Medicine, etc. Pp. 406; 104 illustrations. Chicago: The Year Book Publishers, Inc., 1939. Price, \$3.00.

In this volume, "Office Gynecology," the author takes up many diagnostic or therapeutic procedures in gynecology which could be carried out in a medical office or clinic. Instructions are so definite and concise, the technique is so clearly described, illustrations so well correlated with the text, that the book should be of extreme value to the general practitioner. There are some procedures such as pneumoperitoneum and roentgenography, and colposcopic diagnosis of carcinoma of the cervix, which are beyond the scope of practice of the average practitioner, but are well

included in this book for the benefit of those whose ambulatory patients may be briefly hospitalized. One feels that the presentation of endocrinology in relation to gynecology is well given. It simplifies and will make clearly understandable to many men the confusion of terminology and treatment with which we have been flooded in the last few years. The book gives an excellent résumé of menstrual physiology and irregularities. A most timely chapter on "Premarital Advice" concludes the book. The suggestions contained in this chapter should do much to help the physician in his discussion with the 'about to be married' couple, who seeks his advice. A splendid presentation of the subject. P. W.

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**SLEEP AND WAKEFULNESS.** As Alternating Phases in the Cycle of Existence. By NATHANIEL KLEITMAN, Department of Physiology, the University of Chicago. Pp. 638; 33 illustrations. Chicago: The University of Chicago Press, 1939. Price, \$5.00.

THIS volume presents an exhaustive and competent treatment of the subject. The bibliography contains 1434 references. The discussion is eminently fair, moderately critical, and logically organized. For the researcher in the field the book is indispensable and for his sake we would not delete a line. Yet the final impression is disheartening; few problems have attracted so large a volume of research with so slight an advance toward their solution. G. McC.

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**PRACTICAL OBSTETRICS.** By P. BROOKE BLAND, M.D., Emeritus Professor of Obstetrics, Jefferson Medical College; Consulting Obstetrician, Jefferson Medical College Hospital, Philadelphia, and THADDEUS L. MONTGOMERY, M.D., Clinical Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 877; 502 illustrations, including 27 colored plates. Third edition. Philadelphia: F. A. Davis Company, 1939. Price, \$8.00.

THIS comprehensive volume in practical obstetrics which presents not only the ideas of the authors but many other well tested techniques in the practice of obstetrics, bears evidence of a thorough revision. Again, as in reviews of previous editions, it is warmly commended to the practitioner. P. W.

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## NEW BOOKS.

*Viruses and Virus Diseases.* By THOMAS M. RIVERS, M.D., Sc.D., Director, Hospital of The Rockefeller Institute for Medical Research, New York City. Lane Medical Lecture. (Stanford University Publications, University Series, Medical Sciences, Vol. IV, No. 1.) Pp. 133; 34 illustrations. Stanford University: Stanford University Press, 1939. Price, Paper, \$1.75; Cloth, \$2.50.

*The New International Clinics, Vol. IV, N.S., No. 2, 1939.* Edited by GEORGE MORRIS PIERSON, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 339; illustrated. Philadelphia: J. B. Lippincott Company, 1939.

Fifteen "original contributions," with only two on sulfapyridine, the "clinics" and reviews of urinary lithiasis and ulcerative colitis make up this volume.

*The Medical Clinics of North America, Vol. 23, No. 6 (Philadelphia Number—November, 1939) (Index Number).* Pp. 329; 31 illustrations. Philadelphia: W. B. Saunders Company, 1939.

The symposium in this Philadelphia number includes 8 articles on metabolic diseases—mostly on diabetes. The other 10 articles cover the usually wide range of subjects—congenital syphilis, asthma, renal disease, drug addiction and so on.



*Diagnostic Signs, Reflexes and Syndromes (Standardized).* By WM. EGBERT ROBERTSON, M.D., F.A.C.P., Visiting Physician, Medical Division, Philadelphia General, St. Luke's and Children's, and Northeastern Hospitals, and HAROLD F. ROBERTSON, B.S., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Assistant Visiting Physician, Medical Division Philadelphia General and Methodist Hospitals. Pp. 309. Philadelphia: F. A. Davis Company, 1939. Price, \$3.50.

*The Surgery of Injury and Plastic Repair.* By SAMUEL FOMON, PH.D., M.D., Formerly Major Medical Corps, U. S. Army. Pp. 1409; 925 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$15.00.

*Pathology. An Introduction to Medicine and Surgery.* By J. HENRY DIBLE, M.B. (Glas.), F.R.C.P. (Lond.), Professor of Pathology in the University of London (The British Post-Graduate Medical School); Late Professor of Pathology at the London School of Medicine for Women, etc., and THOMAS B. DAVIE, B.A. (Cape), M.D. (L'pool), M.R.C.P. (Lond.), Professor of Pathology in the University of Liverpool; Late Professor of Pathology in the University of Bristol. Pp. 931; 374 illustrations including 8 plates in color. Philadelphia: The Blakiston Company, 1939. Price, \$10.00.

*The Fight on Cancer* (Public Affairs Pamphlet, No. 38, 1939). By CLARENCE C. LITTLE, Sc.D., Managing Director of the American Society for the Control of Cancer, Inc., and Director of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me. Pp. 31; illustrated. New York: The American Society for the Control of Cancer, Inc., 1939. Price, 10c.

*Harvey Cushing's Seventieth Birthday Party, April 8, 1939.* Speeches, Letters, and Tributes. Pp. 146; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1939, for The Harvey Cushing Society. Price, \$3.00.

*Vitamin D. Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations.* By C. I. REED, A.M., Ph.D., Associate Professor in Physiology, H. C. STRUCK, M.S., Ph.D., Associate in Physiology, and I. E. STECK, M.S., M.D., Instructor in Physiology and in Medicine, Department of Physiology and Department of Medicine, College of Medicine, University of Illinois, Arthritis Clinic, Illinois Research and Educational Hospitals. Pp. 389; 13 illustrations and 36 tables. Chicago: The University of Chicago Press, 1939. Price, \$4.50.

*Handbook of Skin Diseases.* By LEON HUGH WARREN, B.A., M.D., M.Sc. (Med.), Formerly Instructor in Dermatology and Syphilology at the School of Medicine, Temple University; Acting Assistant Surgeon (Dermatology) in the Office of Dermatoses Investigations of the United States Public Health Service, etc. With a Foreword by FREDERICK K. WEIDMAN, M.D. Pp. 321. New York: Paul B. Hoeber, Inc., 1940. Price, \$3.50.

#### NEW EDITIONS.

*The Physiological Basis of Medical Practice.* A University of Toronto Text in Applied Physiology. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), Professor and Head of Department of Physiology; Associate Director of the Connaught Laboratories; Research Associate in the Banting-Best Department of Medical Research, University of Toronto, and NORMAN BURKE TAYLOR, M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.), Professor of Physiology, University of Toronto. Pp. 1872; 497 illustrations and 2 colored plates. Second Edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$10.00.

# PROGRESS

OF

## MEDICAL SCIENCE

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### SURGERY.

UNDER THE CHARGE OF  
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### SOME PROBLEMS OF ACUTE INTESTINAL OBSTRUCTION.

ACUTE intestinal obstruction is a serious disease which is usually accompanied by a high mortality. The sequence of events leading to a fatal outcome has not been clearly understood, nor has any method of treatment been uniformly satisfactory.

A better understanding of various diseases has usually been accompanied by a decrease in the morbidity and mortality associated with these diseases. With a single exception within the last decade this has not been true in acute intestinal obstruction (Table 1). Schramm<sup>41</sup> reported a mortality in acute intestinal obstruction of 73 % before 1873. In a series of cases during the following 10 years the mortality was 58 %. That recent surveys of the subject have not afforded a more optimistic viewpoint is attested by the statement of Miller<sup>32</sup> who estimated in 1929 that the mortality from acute intestinal obstruction was approximately 61 %. The data given in Table 1 indicate the great variation

TABLE 1.—MORTALITY IN ACUTE INTESTINAL OBSTRUCTION.

Author.	Date.	Cases.*	Mortality, %.	External hernia.	Mortality, %.
Gibson <sup>22</sup>	1900	646	47.0	354	34
Scudder <sup>30b</sup>	1908	121	60.0		
Richardson <sup>30b</sup>	1920	118	41.0		
Finney <sup>18</sup>	1921	245	36.0†		
Page <sup>33</sup>	1925	..	.....	539	12.2
Soutar <sup>44</sup>	1925	1655	38.2	1409	19.3
Van Buren and Smith <sup>48</sup>	1925	1089	41.0†?		
Miller <sup>32</sup>	1929	343	60.9†		
Vick <sup>49</sup>	1932	3625	38.8	3267	17.8
McIver <sup>30b,c</sup>	1932	156	44.0	147	18.0
Ssuscewski <sup>45</sup>	1933	121	38.8		
Achmatowicz <sup>3</sup>	1936	138	45.5		
Wangensteen <sup>51</sup>	1939	111	17.1	45	20.0

\* Exclusive of external herniæ.

† Includes external herniæ.

in mortality rates reported by various authors. The data as a whole show little improvement in mortality although our knowledge of the pathologic physiology of gut obstruction has been greatly extended.

McIver<sup>30b</sup> reviewed 3 series of cases over different 10-year periods in the Massachusetts General Hospital; the mortality from 1898-1907 was 60 %; from 1908-1917, 41 %; and from 1918-1927, 44 %.

Several difficulties arise in the analysis of large numbers of cases from the literature. The most obvious of these is that the various series are not always comparable. Acute intestinal obstruction is not a single clinical entity but is actually a collection of conditions with certain common factors. The most obvious are the inability of the gut to propel its content untrammelled throughout its entire length, and the development of distention of the intestine. Variations in etiologic factors, such as the site of obstruction, integrity of blood supply, general condition of the patient before onset, and the length of time elapsed between onset and beginning of treatment, influence the mortality rate regardless of the effects of operative treatment.

Etiologic factors in the initiation of mechanical obstruction of the bowel have long been well understood. Clear descriptions of causation are to be found in the works of Brinton<sup>11</sup> in 1867 and Treves<sup>47</sup> in 1884. Approximately half of all the cases of intestinal obstruction are caused by protrusion of the intestine through external hernial orifices. This has been well borne out by many published statistics. Inguinal and femoral herniæ are the most common offenders in this regard;<sup>30a</sup> according to Vick<sup>49</sup> who studied a large series (6892 cases) approximately 88 % of all obstructions from herniæ were due to incarcerations of gut in these regions. The mortality associated with obstruction due to hernia is low as compared to that due to most other causes, even though the incidence of strangulation is likely to be high. The obvious reason for this lower mortality is that the diagnosis is made early and a standard procedure, early operation, is not usually unduly delayed. In addition, the operation is likely to be simpler since the lesion is not difficult to find. Therefore in reported series which exclude cases caused by external hernia, the total mortality from intestinal obstruction is expected to be higher than in those in which these are included.

Next to external hernia, the most common etiologic factor is adhesions and of these, adhesions resulting from previous surgical procedures form the largest group in this category. McIver<sup>30b</sup> has indicated that in the affected group found early in the postoperative period the mortality is higher than in those cases occurring sometime after operation. This is despite the fact that these cases usually have not left the hospital when they become obstructed and are therefore not to be classed as seeking aid late in the disease. These two conditions, external hernia and adhesions, account for approximately three-fourths of all cases of acute intestinal obstruction.

Obstructions which are likely to be associated with interference with the mesenteric blood supply are as a rule more serious in nature since, in addition to the possibility of necrosis and perforation of the intestine, there is a greater tendency to early toxemia and shock.

The high mortality in most published series is no intimation that decided effort has not been made to understand the cause of death in acute intestinal obstruction. A considerable amount of clinical and laboratory investigation has been expended upon this problem. Three main theses have been advanced to explain the cause of death in this condition.

The oldest theory concerning the cause of death in intestinal obstruction is that a potent toxin is formed. The possibilities for the production of this toxic material are: 1, that the bacteria, particularly *Welch bacilli*, elaborate a specific toxin<sup>34,58</sup> and that specific antitoxins are effective in protecting against this toxin<sup>7</sup> (this viewpoint is contested by Owings and McIntosh<sup>37</sup> and Oughterson and Powers<sup>36</sup> who could find no protective action of *B. Welchii* antitoxin in experimental animals); 2, that the toxin results from an abnormal mucosa or secretions into the gut;<sup>16,55a,b,c</sup> 3, that the toxin arises as the result of bacterial growth in the obstructed gut and is not specific;<sup>13,15,35</sup> 4, that the toxin is formed from putrefaction of intestinal content;<sup>4</sup> and that 5, the symptoms of toxemia actually are the results of bacteria migrating from the obstructed loop causing a bacteremia, as suggested by Borszeky and Gener-sich in 1902.<sup>6</sup> This latter view was promptly and effectively refuted by Clairmont and Ranzi.<sup>13</sup> The nature of the toxic substance is likewise a much debated subject as is also the mode of its transmission from the intestine.

The concept that in simple obstruction death results from loss of fluids and salt has received considerable consideration since it was shown by Hartwell and Hogue<sup>24</sup> and McLean and Andries<sup>31</sup> that animals with obstructed loops of bowel survived longer if a saline solution was administered. That the problem of fluid and salt loss is an important one in these cases has been referred to by Hayden and Orr,<sup>25</sup> Gamble and McIver,<sup>20</sup> White and Fender<sup>56</sup> and many others. That it is the sole cause of death is doubtful since, while survival time is increased by the administration of salt solution, death nevertheless occurs. In those cases in which strangulation is a factor, death occurs early even in animals well hydrated.

The fact that late in the disease patients with acute intestinal obstruction appear similar to patients in shock, has suggested that there is some relationship between the two conditions. The concept suggested by Braun and Boruttau in 1908<sup>9</sup> and occasionally referred to by others<sup>19,57</sup> that the element of shock was quite important in explaining the cause of death in intestinal obstruction, has recently received some attention in German literature. An additional article by Braun in 1925<sup>8</sup> reiterated the concept that associated with occlusion there is strong nervous stimulation which is increased by the addition of physical and chemical stimulation from the altered intestinal content. These stimuli are supposedly mediated not only through reflexes of nerves in the intestine and associated autonomic ganglia, but also act centrally. There results a true picture of shock with associated fluid loss, blood concentration, and capillary stasis.

Gudlad<sup>23</sup> who accepts this concept, has, as recently as 1939, reported on pathologic findings in 190 cases of intestinal obstruction. He feels that his findings support the view that the cause of death is associated with damage to the circulation. However, he also reports changes in the lungs which appear to support the concept of Becher<sup>5</sup> that the lung plays an important rôle in detoxifying substances absorbed from the intestine. Scudder, Zwemer, and Whipple<sup>43</sup> reported results on studies of the potassium content of blood in intestinal obstruction, and point out that acute intestinal obstruction and adrenal insufficiency have many features in common. Scudder, Zwemer, and Truszkowski<sup>42</sup>

reported an elevation in the level of potassium in the blood of cats following obstruction, and suggest that a high potassium level might be the cause of death. This has likewise been reported by Cutler and Pijoan<sup>14</sup> in the dog. However, in the study of human cases Falconer, Osterberg, and Barger<sup>17</sup> did not substantiate these findings. In fact, they noted a fall in the potassium content in the serum and suggest, as did also Scudder, Zwerner, and Whipple,<sup>43</sup> that potassium is actually lost through secretions from the upper intestinal tract.

Within recent years there has been a renewal of interest in the part that distention plays in the cause of death from intestinal obstruction. As an important finding in late cases of intestinal obstruction, distention is stressed as a predominating feature in diagnosis. The rôle that distention plays in the train of events which leads to a fatal outcome in these cases, while referred to by most authors, has not received attention commensurate with its importance until the last decade. Burget, Martzloff, Thornton, and Suckow,<sup>12</sup> Herrin and Meek,<sup>26</sup> and Taylor, Weld, and Harrison<sup>46</sup> stressed the importance of distention *per se*, with regard to the initiation of symptoms and to recovery of animals with experimentally produced obstruction. Burget and coworkers<sup>12</sup> showed that if a closed loop obstruction was kept decompressed no symptoms of obstruction resulted. Herrin and Meek<sup>26</sup> and Taylor, Weld, and Harrison<sup>46</sup> presented experimental data to support the close relationship between the course of events in obstruction and the distention, and indicated that it was possible to cause the entire picture shown by animals with obstructed loops, when no obstruction was present, provided distention of the gut was produced.

Wangensteen and his associates have done much to focus attention upon the rôle of distention as a factor of great importance in acute intestinal obstruction. The initiation of the use of suction drainage in the treatment of acute intestinal obstruction while popularized by these workers, has been sporadically suggested for many years.<sup>52,53</sup> Suction drainage by use of gastric or duodenal tubes is but one method for accomplishing relief of distention of the small bowel. Unfortunately, the method rather than the principle has been regarded as fundamentally important, and we find many who condemn or praise the method without consideration of the basic principles involved. Reiterating these principles, Wangenstein<sup>51</sup> has reported mortality statistics of cases treated by suction drainage which attest to the efficacy of the method but it is to be noted that the cases so treated were a group, most of whom were suitable for this type of treatment, and other cases were submitted to various operative procedures.

In 1938 Abbott and Johnston<sup>2</sup> reported the use of intestinal intubation in the treatment of simple intestinal obstruction by the use of a tube developed by Miller and Abbott.<sup>33</sup> The rationale of its use was based on the proposition that the distended intestine could be decompressed better with suction applied directly above the point of obstruction than at higher levels. This, in effect, is tantamount to an enterostomy without the necessity of an operative procedure. In addition to drainage from a vantage point it permits the feeding of the patient. Further studies with this method have indicated its usefulness, not only with regard to the treatment of intestinal obstruction,

but also for localization of the obstructing lesion<sup>1a,b,27,28a,b,29</sup> and for the preparation of the patient for operation. Sufficient experience has been gained with the use of intestinal intubation in the treatment of simple intestinal obstruction and adynamic ileus to illustrate its efficacy. In several clinics where it has been used extensively, but judiciously (Hospital of the University of Pennsylvania, Detroit Receiving Hospital, and Presbyterian Hospital in New York), there has resulted a marked reduction of the mortality rate from acute intestinal obstruction. For the past 2½ years the mortality from small intestinal obstruction at the Detroit Receiving Hospital, including all cases of intestinal obstruction whether the obstruction contributed to the death or not (except those due to strangulated external hernia) has been approximately 23.9%. The mortality from simple acute obstruction treated by intubation was 9%. Similar good results have been attained at the Presbyterian Hospital.<sup>54</sup> The limitations of the method and difficulties of its use as well as its advantages are set forth in publications of Abbott and his associates<sup>1a,2</sup> and Johnston and his associates.<sup>2,28a,b,29,39</sup>

It is not possible at present to obtain an adequate appraisal of the effect which the judicious use of suction drainage has had on the mortality from small bowel obstruction. It is much too early, since its place in therapy was enunciated by Wangensteen and since the introduction of drainage from the lower reaches of the bowel, to allow for large series to have been reported. It is to be recognized as significant that in comparison to older statistics, those presented by Wangensteen and associates<sup>51</sup> have a decidedly lower mortality, and we have been able to bring about a further decrease in the mortality of our own cases. It is worthy of note that Wangensteen<sup>51</sup> has surveyed all types of cases of small bowel obstruction and reports a mortality of 17.9%, reducing the mortality from obstructions within the abdomen to below that commonly attained in those cases associated with external hernia. The cases reported by Wangensteen were not a personal series but were cared for by several individuals. However, this group of surgeons must recognize the place of suction drainage in the broad problem of the therapy of intestinal obstruction, based on an understanding of the pathology and physiology involved. The problem of treatment of this condition must be based on principles involved without regard to strict adherence to any method. The well-known saying that "the sun should never set on an unoperated case of intestinal obstruction" is as erroneous and as productive of poor results as such general dicta are likely to be, if followed strictly. Wangensteen<sup>51</sup> has pointed out that there is a mortality of treatment as well as of disease, a fact which is too often ignored. Treatment carried out on the basis of dicta, or fixed routine, without regard to the pathologic lesion and physiologic principles involved, and without the consideration of obstruction of the bowel as a diversified problem, must lead to many unnecessary fatalities.

An additional method of decompressing the distended intestine has been suggested by Rosenfeld and Fine<sup>40</sup> who found that in cats it was possible to cause a marked decrease in intraluminal pressure produced by distention of air or nitrogen if the animals were made to breathe pure oxygen. This procedure offers promise for use in intestinal ob-

struction, even though it is likely to be slow in its action in decreasing the amount of gas present, because of the salutary effects offered in more effective oxygenation in a patient whose respiratory activity is hampered by distention.

Regardless of the possibilities for the reduction in mortality from intestinal obstruction by careful consideration and use of suitable methods of treatment, it is not likely that the mortality from this condition will be lowered materially until the importance of early diagnosis is universally recognized.<sup>50</sup> Within a few hours after the onset of obstruction, when distention is likely to be slight, operation is attended by low mortality.<sup>10,32</sup> When distention is marked, dehydration present, and changes in blood chlorides and urea are marked, the difficulties of treatment are greatly increased. It is well to point out that in addition to the recognition of the early symptoms of intestinal obstruction the Roentgen ray offers early diagnostic aid. The use of contrast media is not necessary, but actually contraindicated early in the disease. In fact, Roentgen ray without contrast media offers the only early laboratory finding of any advantage, and should be utilized in all suspected cases. While the upright film may reveal fluid levels and indicate the presence of obstruction, the supine film will in many instances indicate the level of the obstruction. When the diagnosis of obstruction is established early, before marked distention and dehydration are present, operation ought not to be delayed.

Early diagnosis and treatment, so important in simple acute obstruction, becomes imperative in those cases where there is interference with the mesenteric blood supply, not only because of the possibility of releasing the occlusion to the vessel early, thereby preventing necrosis of the bowel, but for the prevention of the development of the severe toxemia which is so rapidly fatal. The early differentiation between simple and strangulated obstruction is not easy. The diagnosis of strangulation is based on the severity of the onset, the rapidity of progression of symptoms, evidence of a localized gas-filled loop, and symptoms out of proportion to the amount of distention present. Increasing pulse rate, falling blood pressure, and presence of localized tenderness are likely to be found late and should always suggest strangulation. Gatch<sup>21</sup> has suggested that it is possible to treat such patients without operation until the strangulated loop becomes well walled off as is practiced in cases of appendiceal abscess, but we have not felt that it is wise to defer operation in cases of suspected strangulation. Preparation by blood transfusion, intravenous saline solutions, and the insertion of a tube at least into the stomach, need not delay operation long and are important aids.

Consideration of the importance of distention as the initiating factor in the sequence of events following simple acute obstruction of the bowel does not imply any particular form of therapy. Relief of distention can be brought about by operation or by removal of the distending content from within the bowel by means of intubation. Which of these methods is to be used depends upon the problems presented by the patient and not by custom. There have undoubtedly been instances where an attempt has been made to apply suction drainage for treatment of intestinal obstruction without regard to the problem presented by the patient and it is to be expected that such attempts

will be disheartening. The concept that suction drainage is a specific regimen for intestinal obstruction is but little less dangerous than the concept that early operation is indicated in all forms of intestinal obstruction. It is only by early diagnosis, a consideration of the underlying principles involved, the conscientious appraisal of the patient, and the utilization of the best available forms of treatment—that the unnecessarily high mortality from intestinal obstruction will be effectively lowered.

I. S. RAYDIN, M.D., AND C. G. JOHNSTON, M. D.

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## OPHTHALMOLOGY

UNDER THE CHARGE OF  
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**THROMBO-ANGITIS OBLITERANS OF THE RETINAL VESSELS.**

IN this section for August, 1935, the subject of recurrent hemorrhages into the retina and vitreous was reviewed. At that time it was stated that in most cases of this syndrome in the young adult the causative lesion was thought to be tuberculous periphlebitis of the retinal veins. Attention was called to the occurrence of an essentially identical lesion in patients with diabetes mellitus in whom no definite etiologic factor aside from the diabetes could be discovered. Recently Friedenwald has called attention to the possibility that the basic cause of the hemorrhages in this latter group of cases is an increase in capillary fragility dependent on an improper utilization of vitamin C, associated in some way with a deficiency in vitamin B complex. It was pointed out that in certain non-diabetic cases in which the diagnosis of tuberculosis of the retinal vessels seemed unlikely, the cause of the lesion had been assigned by various authors to focal infection and rather vague endocrine or circulatory disturbances. A few cases can be proved to be due to syphilis. In the majority of cases when the vitreous is sufficiently clear to allow careful study of the retina, local lesions in the retinal vessels, usually the veins, can be seen to be the source of the bleeding. In a fairly large number, however, the exact cause of the local vascular lesion remains in doubt. At the time of writing this review I was not acquainted with the studies of Marchesani<sup>9a,b</sup> which were published in the latter part of 1934 and in 1935.

It is of interest that in reporting on a case of hemorrhage into the vitreous before the Ophthalmological Society of the United Kingdom in 1881, Jonathan Hutchinson<sup>3</sup> stated that his patient, a young man of 24, had had frequent epistaxis, cold feet, vague pains simulating gout, pain in the heel which prevented him from walking at times, "rheumatic" pains in the fingers and toes, and a "numb tingling" in the thumbs. Marchesani was impressed by the difficulty of demonstrating the presence of tuberculosis in other parts of the body in the majority of his patients with recurrent hemorrhages into the vitreous. He noted that many of them complained of symptoms similar to those described by Hutchinson and, in addition, often of transitory severe cyanosis of the extremities and trophic disturbances in the nails and skin. Pulsations were absent in one or more of the arteries of the lower extremities of a number of the patients. All of them showed definite changes in the nail-fold capillaries, such as widening of the intercalary space, dilatation of the venous loops, and spontaneous capillary hemorrhages. In his opinion, a disease which affects only the vascular system, runs its course without marked evidences of inflammation, and does not lead to a destructive lesion of the tissues of the eye cannot be considered to be tuberculosis. Because of the evidences of a more or

less generalized disturbance of the vascular system in these individuals, Marchesani believes that the vascular lesions in the retina responsible for recurrent hemorrhages into the vitreous represent an ocular manifestation of thrombo-angiitis obliterans (Buerger's disease). He admits that the coincident occurrence of retinal periphlebitis with manifest gangrene of the extremities is rare. He based his conclusions on the study of a series of 22 patients, 2 of whom had gangrene of toes and 1 gangrene of fingers; 19 of the patients were thought to have evidences of latent Buerger's disease.

Marchesani further supported his views by his interpretation of the histologic findings in the eye of one of the patients with gangrene. He found that the lumens of the smallest retinal vessels were variably narrowed as a result of a homogeneous structureless swelling of the subendothelial tissues. In some of the larger vessels, both arteries and veins, the endothelial layer was destroyed and the lumen was filled with a cell-poor or cell-free fibrin-like mass of homogeneous or network structure. Around these vessels there had been some extravasation of red blood cells and some increase in the glial fibers with only a few cells of inflammatory type. In other vessels the lumen was filled with granulation tissue rich in cells of endothelial character with some evidences of recanalization. There was some splitting up of the lamina elastica but the rest of the wall was not abnormal. Vessels in the iris and ciliary body were involved as well as those in the retina. In some of the vessels at the limbus a non-specific perivascular infiltration with round cells was present. According to Marchesani, these vessel changes are similar to those described by other authors in the extremities, internal organs and brain in patients with Buerger's disease. Marchesani discussed also the histologic findings in a case reported by Fleischer as one of tuberculosis of the retina. Marchesani thought that the endothelial proliferation with scattered points of occlusion of the lumen and the cellular proliferation in the vessel sheaths described by Fleischer were evidence of thrombo-angiitis obliterans, and that the nodules considered by Fleischer to be tubercles were really occluded vessels.

In 1938 Marchesani<sup>8c</sup> reported the histologic findings in 2 other eyes, the lesions in which had been diagnosed by him as thrombo-angiitis obliterans of the retinal vessels. In one with recurrent hemorrhages into the vitreous the retinal vessels near the disk showed hyaline thickening of the walls. This hyaline thickening increased in degree in the distal parts of the vessels, especially the veins, so that in some spots the lumen was almost obliterated. In most of the peripheral vessels, however, the lumen was completely filled with a cell-poor fibrin-like tissue with occasional cellular proliferations suggesting recanalization of the lumen. In the other, apparently a postspastic occlusion of the central artery of the retina, the central artery of the retina and its branches showed severe wall changes with marked narrowing of the lumen but without complete closure at any point. These changes were in part in the nature of hyaline thickening with localized endothelial proliferation and in part apparently homogeneous thrombus formation in the lumen firmly attached to the wall. Similar changes were found in the cerebral vessels.

In 1934 Stauder<sup>14</sup> called attention to a group of cases simulating mul-

multiple sclerosis which he believed to be really thrombo-angiitis of the cerebral vessels. In a paper published in collaboration with Marchesani<sup>9</sup> in 1935, Stauder reported that 3 of Marchesani's 20 patients with primary symptoms of retinal periphlebitis showed this central nervous system syndrome of atypical multiple sclerosis. Also 5 cases which were seen primarily by the internist or neurologist showed lesions suggestive of thrombo-angiitis of the retinal vessels. In 3 of these the typical syndrome of retinal periphlebitis with recurrent hemorrhages into the vitreous and retinitis proliferans was present. In Stauder's opinion, the 2 cases reported by Löwenstein as tuberculosis of the cerebral vessels and of the eye and the 6 cases of ophthalmo-encephalomyelitis reported by ter Braak and van Herwaarden, 2 of which showed typical retinal periphlebitis, are further examples of cerebral and retinal thrombo-angiitis obliterans.

Marchesani's conception of the nature of this rather puzzling syndrome of recurrent hemorrhages into the vitreous is at least an interesting one even if it cannot be considered as definitely proved as yet. Personally, I have seen thrombosis of the retinal veins in a few of a rather large series of patients with typical Buerger's disease of the extremities. Also 1 patient, seen originally because of recurrent hemorrhages into the vitreous, returned several years later with the characteristic picture of thrombo-angiitis of the lower extremities. Although he had no subjective eye complaints at the second visit and no hemorrhagic extravasations were found in the vitreous, active periphlebitis with hemorrhage was still present in each retina.

Since Marchesani's original publication, several other authors have reported essential agreement with his conclusions. In 1935 Ludwig<sup>7</sup> reported a case of recurrent hemorrhage into the vitreous on the basis of disease of the smaller arterial and venous branches with aneurysmal dilatation and new vessel formation, but without perivascular lesions or focal lesions in the retina or choroid. This patient was believed to have Buerger's disease because of the additional presence of paresthesias of the hands and feet and changes in the capillaries of the nail-fold characteristic of a vasoneurosis. Also in 1935, Gilbert<sup>1</sup> reported 2 cases, 1 with a closure of the inferior temporal branch artery and 1 with perivasculitis of the inferior temporal branch artery and vein, both of whom developed later thromboses in the lower extremities. He stated that Buerger's disease must be thought of as the possible etiologic factor in otherwise unexplained instances of closure of the central or branch arteries of the retina. In 1936 Mikuni<sup>11</sup> stated that in his clinical observations retinal periphlebitis and thrombo-angiitis obliterans in other parts of the body were at times coincident. He was able to find evidences of Buerger's disease in 2 of 7 patients with retinitis proliferans. In his ophthalmoscopic studies of 5 patients with Buerger's disease, he found retinitis proliferans in 1. In 1937 Lisch<sup>6a</sup> reported a closure of the central artery of the retina in a man 33 years of age, which he believed to be due to thrombo-angiitis obliterans since the man had gangrene of the toes, barely palpable dorsalis pedis arteries, and changes in the nail-fold capillaries. In 1937 Schmelzcr<sup>13</sup> reported that he had examined 6 cases of classical thrombo-angiitis obliterans with gangrene of the extremities, in none of whom was there evidence of recurrent hemorrhages into the vitreous. One of the patients, how-

ever, had had a closure of the central artery of the right eye 4 years before. Schmelzer thought, therefore, that closure of the central artery of the retina or one of its branches in a relatively young, otherwise healthy adult might be an early sign of a progressive thrombo-angiitis obliterans. In 1938 van Rijsewijk<sup>17</sup> suggested the possibility of Buerger's disease in a case with recurrent hemorrhages into the vitreous and Jacksonian epilepsy. Radnót stated that Lange and Birnbaum also confirmed Marchesani's findings.

Two histologic studies also have been published in which the authors agree with Marchesani's interpretation of the lesions in the retinal vessels. In 1937 Uyama<sup>16</sup> reported 2 cases which he diagnosed clinically as thrombo-angiitis obliterans of the retinal vessels. In one of these cases histologic examination showed that the walls of the smaller retinal arteries were thickened, the lamina elastica hyperplastic, and that there were increased collagenous and elastic fibers in the ground substance of the intima. The lumens were lined by normal or swollen endothelial cells but were markedly narrowed or closed by the thickening of the walls. The lumens of the larger arteries were filled with blood corpuscles and homogeneous fibrin-like masses containing some epithelioid cells suggestive of thrombosis. The walls of the veins were thickened but the lumens were not occluded and the capillary walls were thickened also. Uyama thought that this picture corresponded to the first form of intimal proliferation described by Jäger in endangitis obliterans. In 1938 Maul<sup>10</sup> reported the case of a man, aged 56, who suffered from definite Buerger's disease of the extremities, and who had a unilateral optic atrophy secondary to closure of the central artery of the retina. Histologically, the central artery of the retina, and to a less extent the central vein, showed subendothelial proliferation and patchy endothelial proliferation. In the central artery there was a homogeneous firmly attached thrombus. Similar changes were present in the walls of the cerebral vessels.

There has been also considerable opposition to the acceptance of Marchesani's views on the basic nature of these perivascular and occlusive lesions of the retinal vessels, particularly by those authors who believe that recurrent hemorrhages into the vitreous in young adults are due always to tuberculosis of the retinal vessels. In 1935 Kokott<sup>5</sup> reported that among 5 clinical cases of retinal periphlebitis with recurrent hemorrhages into the vitreous 2 were definitely proven to be tuberculous and 1 was probably tuberculous. Two of the patients had no demonstrable systemic disease. In none were there any signs of Buerger's disease. Also in 1935 Knapp<sup>4</sup> reported no evidence of Buerger's disease in 1 case and von Hippel<sup>2</sup> stated that among 11 cases of Buerger's disease of the cerebral vessels reported by Jäger and confirmed at necropsy, there was no instance of retinal periphlebitis. In 1937 Radnót reported that among 6 cases of retinal periphlebitis none showed any clinical evidence of Buerger's disease while 3 showed healed pulmonary tuberculosis. In the discussion Radnót stated that Löwenstein, Petragani, Schreck, Bonnet, Paufigue and Vogt had not found any evidence of Buerger's disease in their patients with retinal periphlebitis. In 1939 Lisch<sup>6</sup> studied ophthalmoscopically 35 cases of various forms of peripheral vascular disease, among which there were 5 cases of thrombo-angiitis obliterans. He found no evidence of retinal periphlebitis in

any of these cases, and consequently does not believe that vascular disease of the Buerger type plays an important rôle in the etiology of recurrent hemorrhages into the vitreous.

Considerable histologic evidence also has been adduced to controvert Marchesani's conception. It is well known that perivenous lesions can be produced in the retina of experimental animals by the injection of living tubercle bacilli into the carotid artery. Recent confirmation of these results was furnished by Uyama who first sensitized rabbits by the subcutaneous injection of tuberculous antigens and then injected living tubercle bacilli into the left heart. In his series of 26 animals so treated, 4 developed retinal periphlebitis. The lesions showed lymphocytes and endothelial cells but no giant cells or caseation. In 1935 von Hippel examined histologically an eye enucleated because of secondary glaucoma following recurrent hemorrhages into the vitreous. He found short stretches of two retinal arterics closed by intimal proliferation in which epithelioid and giant cells were present. The retinal veins showed perivascular infiltration, partly mononuclear round cells, partly nodular collections of epithelioid cells, round cells, and occasional giant cells. In some spots the lumen of a vessel was completely or almost completely closed by cellular proliferation of indeterminate type, possibly an organized but not a recanalized thrombus. In the choroid there was a characteristic tuberculous nodule with caseation necrosis of the overlying retina. A vessel in the iris was completely closed by lymphocytic infiltration. There was round cell infiltration of the wall of the central vein of the retina with narrowing but not obliteration of the lumen. No tubercle bacilli were demonstrated, but the case was considered to be definitely ocular tuberculosis. Von Hippel considers Buerger's disease to be a non-specific occlusive and inflammatory disease of the vessel walls. He does not deny that such non-specific vessel wall disease may occur in the retina. But, since he can find this type of vessel lesion in cases which show definite tuberculosis in other tissues of the eye, he is inclined to believe that tuberculosis is the etiologic factor in the majority of cases of this type.

In 1937 Suganuma<sup>15</sup> reported the case of a girl, aged 21 years, who had recurrent hemorrhages into the retina and vitreous of the right eye with retinitis proliferans. In the left eye there was a sclero-kerato-iritis, clinically of tuberculous type. By roentgenogram there was infiltration of the apices of both lungs. Later iritis and secondary glaucoma developed in the right eye and the eye was enucleated. Histologically, there was a periphlebitic patch in the equatorial region of the retina. This was made up centrally of epithelioid cells and peripherally of round cells with giant cells in the intermediate zone. The vein was not thrombosed. There was an exudative mass of epithelioid cells which broke through into the vitreous. On the inner surface of the retina there was a proliferated band of connective tissue, glial fibers and blood-vessels. A small patch of epithelioid cells was found surrounding a choroidal artery. In the anterior segment of the eye nodules of epithelioid and giant cells were present in the iris, ciliary body and cornea. The case was considered to be one of ocular tuberculosis.

Also in 1937 Radnóti reviewed the arguments for and against the occurrence of the Buerger type of thrombo-angiitis obliterans in the retinal vessels. Noting that Gilbert had demonstrated tubercle bacilli

in a case of retinal periphlebitis, she makes a distinction between lesions which are primarily perivascular in type and location and those which affect the vessel wall itself primarily. She reports on the histologic examination of 5 cases. Four of these cases showed definite periphlebitic lesions which were considered to be tuberculous. The inflammatory changes were located entirely outside the vessel wall, the wall itself being unaffected. The lumen of the vessel was compressed or even obliterated by the pressure of the granulation tissue around the periphery of the vessel. In the fifth case there was a primary lesion of the vessel walls, especially of the media. There was a hyaline degeneration of the middle layer leading in places to closure of the lumen. In other places the vessel seemed to be converted into a nodule of non-specific granulation tissue. There was no apparent lesion of the intima. In Radnót's opinion the lesions in this last case might be considered to simulate the picture of thrombo-angiitis obliterans of the peripheral vessels.

In summary, it might be said that in the vast majority of the cases, at least, the basic local lesion underlying recurrent hemorrhagic extravasations into the vitreous is a diseased condition in the walls of the retinal vessels, predominantly or primarily in most, if not all instances, in the veins. The distinction between a primarily perivenous and a primarily venous or arterial lesion may be an important one from the etiologic standpoint. An attempt should be made to differentiate these lesions ophthalmoscopically where the vitreous is sufficiently clear to allow careful study of the retinal vessels. A certain number of the cases, particularly of those of perivenous type, may be due to tuberculosis, either primary in the retina or secondary to a hidden or latent focus of tuberculosis in the choroid. In perhaps a larger number of cases in which tuberculosis cannot be demonstrated elsewhere in the body, there may be a primary non-specific inflammatory or degenerative lesion of the vessel walls. This lesion may be the retinal counterpart of Buerger's disease and may be confined to the retinal vessels or at times may be associated with similar lesions in other parts of the body. In certain cases of closure of the central artery of the retina, the basic lesion may be a primary disease of the vessel wall simulating or related to thrombo-angiitis obliterans.

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## PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF DECEMBER 19, 1939

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**Distribution of Water and Serum Electrolytes in Experimental Diabetes Mellitus.** F. WILLIAM SUNDERMAN and F. C. DOHAN (Department of Research Medicine, Pepper Laboratory and Cox Institute, University Hospital). Measurements of serum volume, extracellular fluid and concentrations of serum components were made in depancreatized dogs that had been permitted to go into ketosis following the withdrawal of insulin. Since the depancreatized animals suffered marked reduction in body weight, for comparison similar measurements were made following ketosis from simple starvation.

In the depancreatized dogs the average serum volume calculated in relation to the body weight was approximately 29% greater during ketosis than during the control period, although the total serum volume was approximately 10% less during ketosis than during the control period. In ketosis from starvation the total serum volume was decreased in proportion to the reduction in weight and within the limits of error of the measurements the serum volume in relation to body weight was unchanged.

The actual quantities of total base, chloride, bicarbonate and protein in the circulating serum were decreased during ketosis in the depancreatized animals although the amounts of these components, with the exception of bicarbonate, when expressed in relation to body weight were all increased.

The studies suggest that the dehydration observed in experimental diabetes mellitus induced by pancreatectomy in dogs is not made at the expense of serum volume or of the extracellular fluids but rather at that of the intracellular fluids.

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**Mechanism of the Diuresis Produced by Acacia.** ARNOLDUS GOUDSMIT, JR. (Laboratory of Physiology, School of Medicine, University of Pennsylvania). The present report incorporates the results of clinical and experimental observations gathered at the Mayo Clinic and Foundation, in collaboration with Drs. Binger, Power, Keith and Bollman. Injections of acacia may be followed by the mobilization of edema fluid and its elimination with the urine in patients suffering from the nephrotic syndrome. A good diuretic response was obtained in 36 out of 40 consecutive cases in which this form of treatment was used.

The colloid osmotic pressure of the serum examined after completion of a course of injections of acacia was increased as compared to its level before treatment in only 43% of 28 cases in which it was determined. It was essentially unchanged in 39% and actually decreased in 28%. As a consequence of the injection of acacia the volume of the plasma increases, its constituents are diluted and it depends on the relationship of the diminution of concentration of the serum proteins and the concentration of acacia in the plasma what net changes in

colloid osmotic pressure actually take place. There was no correlation between the direction of the change of colloid osmotic pressure and the clinical response (diuresis or absence of it).

Experiments on dogs were therefore performed, testing whether acacia might alter the permeability of the kidney. It was found that the rate of glomerular filtration (creatinine clearance) was essentially unchanged; but the rate of excretion of chloride was significantly increased, an average of 189%. Subsequently, a study of patients receiving acacia revealed similar increases in the absolute amount of chloride excreted per 24 hours, and sometimes also of its concentration in the urine.

It is well to remember that a very important disturbance of the function of the kidney in the nephrotic syndrome is its inability to excrete all sodium chloride and water ingested. The consequent accumulation of these substances leads to the appearance of edema. It is difficult to conceive how the diminished concentration of protein in the serum and the decreased colloid osmotic pressure could be held directly responsible for what appears to be an abnormally large tubular reabsorption of water and sodium chloride. Whatever its explanation, it would seem that acacia helps in the reduction of tubular reabsorption of chloride and water to a more normal level.

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**Studies on the Molecular Weight of Diphtheria Toxin, Antitoxin and Reaction Products.** A. M. PAPPENHEIMER, JR. (Antitoxin and Vaccine Laboratory, Jamaica Plain, Mass., and Department of Bacteriology, University of Pennsylvania). Preparations of diphtheria antitoxic horse pseudoglobulin have been made of which 43.5% of the nitrogen is specifically precipitable by toxin. These preparations behave in every way, except immunologically, as a single molecular species; they are extremely homogeneous by sedimentation, electrophoresis and diffusion. Although the molecular weight of antitoxin as calculated from the sedimentation-diffusion data does not differ significantly from that of normal horse serum globulins, the electrophoretic mobility does differ from those of normal serum components.

The molecular weight of diphtheria toxin is 70,000 and of antitoxin is 150,000.

From ultracentrifuge studies on the two reactants and on mixtures of toxin and antitoxin in soluble inhibition zones, the average molecular composition of the specific floccules at certain reference points throughout the equivalence zone and the maximum "valence" of toxin and antitoxin with respect to each other have been calculated.

The toxin-antitoxin complex is aggregated even in soluble regions of toxin and antitoxin excess. The equilibrium between aggregated and unaggregated forms is dependent on the concentration of the specific protein in excess.

The significance of the results was discussed in relation to antigen-antibody reactions in general.

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**Some Cellular Diffusion Processes Involving Hydrolytic Membrane Equilibria.** M. H. JACOBS and A. K. PARPART (Department of Physiology, University of Pennsylvania, and Department of Biology, Princeton



University). Hydrolytic membrane equilibria are well illustrated by the behavior of the erythrocyte in the presence of various ammonium salts, singly and in different combinations. Three chief types of such salts may be distinguished: *a*, those of weak, so-called penetrating acids, which enter all cells with ease by a "molecular" type of penetration; *b*, those of strong mineral acids, to whose anions the erythrocyte is permeable, which enter it by a "molecular-ionic" mechanism consisting of the penetration of  $\text{NH}_3$  followed by an exchange of  $\text{OH}'$  ions for other anions; and, *c*, those of acids to whose undissociated molecules and anions the erythrocyte is relatively impermeable.

In a mixture of two salts of types *a* and *c* the former in general tends to become unequally distributed between the cell and its surroundings in a manner that in some respects resembles and in others differs from the well-known Gibbs-Donnan ionic equilibrium. This unequal distribution explains the rapid but limited swelling that occurs on adding a salt of type *a* to erythrocytes suspended in solutions of ammonium citrate, but not of  $\text{NaCl}$ .

A mixture of salts of types *a* and *b* produces a similar swelling, which may be followed by exchanges of anions, thus permitting the process to proceed indefinitely. The rapid rate of entrance of  $\text{NH}_4\text{Cl}$  into erythrocytes by this mechanism in the presence of low concentrations of bicarbonates, sulphides and cyanides may in a certain sense be considered to be a catalyzed diffusion process.

The addition to a suspension of erythrocytes in ammonium citrate at pH 7 of a little saturated  $\text{NaCl}$ , by furnishing ions for which  $\text{OH}'$  can be exchanged, may cause marked swelling of the cells in spite of the increase in the external osmotic pressure. In the analysis of processes involving the penetration of ammonium salts, use may advantageously be made of the retardation of ionic exchanges, but not of certain types of molecular penetration, by butyl alcohol and related substances.

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ORIGINAL ARTICLES.

THE RENAL LESION IN OBSTRUCTIVE JAUNDICE.

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"CHOLEMIC nephrosis" has received little attention from those interested in the problems of bile tract disease even though reports in the literature suggest that renal injury secondary to hepatic disease or injury may be more frequent than is generally believed. We have attempted to determine the importance of the renal injury in a group of patients with obstructive jaundice in the surgical wards of this hospital and in the experimental animal following common duct obstruction and cholecystectomy.

Wilensky,<sup>28</sup> in a recent review of the subject of "liver death," points out that the hepatorenal syndrome, in addition to its incidence in liver and biliary disease, has been seen to follow operations for other conditions such as carcinoma of breast, gastric ulcer and so on; following the use of certain drugs; in the toxemia of pregnancy, thyrotoxicosis, burns and intestinal obstruction. Wilensky stresses the phylogenetic relation between the liver and kidney, which in certain mammals does not involute, leaving a portal vein to the kidney. Anastomoses between the vessels to the liver and kidney are at times observed in both animal and man.

Elsom,<sup>6</sup> studying the renal function of 16 patients with obstructive jaundice and 1 with arsenical hepatitis with the Addis method,

found an increase in casts, epithelial cells and white blood cells, and in erythrocytes in 8 of the patients, and an increase in albumin in only 4 patients. Elsom found that the absence of albuminuria is a differential diagnostic point between "cholemic nephrosis" and other forms of nephrosis. Blood urea nitrogen determinations ranged from 15.5 to 28.1 mg. % in 8 patients and the urea clearance ranged from 80% of normal to a significant reduction in half the cases.

The occurrence of uremia in hepatic disorders was reported as early as 1876,<sup>24</sup> although at that time renal involvement was thought to be absent. Helwig and Schutz<sup>11a</sup> reported severe renal damage with fatal uremia in 2 cases of liver disease (1 neoplastic, the other associated with severe trauma of the liver). They also reported 4 cases of gall bladder disease with evidence of renal damage. They believed that the damage was not due to an increase in the bile salts in the blood since only 2 of the patients were jaundiced. The increase in bile salts in the blood after obstructive jaundice lasts for only a few days while the nephrosis persists during the period of jaundice. Bartlett<sup>2</sup> found 6 patients of 56 consecutive cases with bile tract infection who had renal damage with oliguria. Not all of these were jaundiced. Meyers and co-workers,<sup>16</sup> in a study of 21 cases of jaundice, found 7 with high blood urea nitrogen figures. Eiss,<sup>5</sup> Schutz and associates<sup>19</sup> and Rowntree<sup>18</sup> have noted uremia in patients following biliary surgery. Others<sup>7 10 15 22 23</sup> have noted evidence of renal injury ranging from albuminuria to uremia and death in disease of, and trauma to, the liver.

Wilensky,<sup>26a</sup> in a study of the relation of nitrogen retention to liver and biliary tract disease, found that the blood urea nitrogen was elevated: (1) in 67% of mild grades of biliary tract disease without complications; (2) in 86% of mild or moderately severe disease with jaundice; and (3) in all but 1 case of mild grades with jaundice and nephritis.

The mechanism involved in renal damage following common duct obstruction or liver injury is not clearly understood. Lichtman and Sohval<sup>13</sup> believe that the anuria and azotemia are due to a pre-renal deviation of fluids. They feel that this is the result of disturbances of those liver functions which are concerned with water and mineral balance and water is not available for renal excretion. It is their opinion that operation, jaundice, shock, decompression and vomiting are not essential in producing renal lesions and that use of the term "hepatorenal" syndrome should be avoided. Stewart and Cantarow,<sup>21</sup> following the intravenous injection of dogs with sodium dehydrocholate, an unnatural bile salt, were able to produce severe renal lesions demonstrating regressive and regenerative changes in the tubules.

In common duct obstruction there is usually some hepatocellular damage and it is not unlikely that other substances toxic to the kidney may be released from the injured liver cells. Ravdin<sup>17</sup>

found an increase in histamine and choline in livers of dogs in which the common duct had been ligated over a period of days.

Boyce and McFetridge,<sup>3</sup> following a clinical and experimental investigation of the mechanism of so-called "liver death," came to the conclusion that the hepatorenal syndrome is due to the release of the common duct obstruction. This, they believe, permitted the escape of a toxin which, acting upon an overtaxed kidney, causes a breakdown of the convoluted tubules. This thesis is also held by others.<sup>11b 19</sup>

Heyd<sup>12a b</sup> is of the opinion that the kidney lesions and the anuria seen in liver disease are unrelated to the liver. He divides "liver deaths" into three groups: 1, hepatic exhaustion due to surgical intervention; 2, hepatic failure following release of the obstruction in jaundiced patients which causes a reactive hyperemia in an already compromised liver; 3, pancreatic intoxication in disease of the common duct and pancreatitis without jaundice. Dourmashkin<sup>4</sup> presented an interesting report on 2 patients with coexisting hepatic cirrhosis and urethral stricture, who, following urethral instrumentation, developed an acute hepatorenal syndrome and died. Their urine showed albumin and red cells and the one patient at autopsy showed epithelial degeneration of the kidney. Another patient, assumed to have cirrhosis, developed a mild icterus following intra-ureteral manipulation for a stone and recovered. In a review of 500 deaths following operations on the gall bladder and bile ducts, Stanton<sup>20</sup> reported that 24 were due to renal failure.

We feel that the renal lesion in common bile duct obstruction and in instances of more severe liver damage should not be considered as a minor complication, but as a major one. It is true that in most instances permanent injury does not occur if relief of the aggravating condition is afforded promptly, but there is a not inconsequential group which goes on to anuria and a uremic death.

**Pathologic Anatomy.** The pathologic change of the kidney of "cholemia nephrosis" has been described<sup>25</sup> as being confined mainly to the tubules. These exhibit dilatation with a narrowing and degeneration of the epithelial cells. There is occasionally partial obstruction of the tubules, which contain much granular debris and occasional casts. Bile pigment may be seen in the epithelial cells and in the intratubular spaces. There are often localized areas of fibrosis and edema in the interstitial tissue. In other instances one finds sclerotic patches with hyalinized glomeruli and atrophic tubules. As a rule the glomeruli are normal, but may show an increase in, and some swelling of, the endothelial cells. Granular debris is often present in Bowman's capsule and there may be irregular thickening of the membrane.

Lieber and Stewart<sup>14</sup> classified microscopic renal changes in patients with bile duct obstruction in their material as follows: (1) In complete and permanent obstruction of the common duct

due to primary carcinoma of the pancreas a few regressive changes and much green, yellow and black pigment, although there is not much bilirubin; (2) in carcinoma of the pancreas with death following surgical decompression, regressive changes are prominent, although there is diminution of renal pigment; (3) in obstructive jaundice due to calculi with death following decompression, regressive changes more marked than in (2); (4) in calculous disease without jaundice with death following surgical procedures, damage is less than in (2) and (3).

**Clinical Studies.** In order to investigate the incidence of renal injury following bile duct obstruction the histories of 32 patients with obstructive jaundice on Surgical Divisions "B" and "E" were studied. Most of these were cases of calculous obstruction, although 3 had pancreatic lesions, 2 stricture of the common duct, and 1 a carcinoma of the ampulla of Vater. All were jaundiced for periods ranging from 3 days to 9 months. All patients came to operation and 5 died.

Six of the 32 excreted urine with a specific gravity of 1.015 or less, and 16 excreted urine with a specific gravity of 1.020 or less. At least a trace of albumin was present in the urine in every case; it was present in a moderate amount or more in 17. This is not in accord with Elsom's<sup>6</sup> statement that absence of albuminuria is a distinctive feature of "cholemic nephrosis." Casts were seen in the urine of 13 patients, although not in large numbers except in 5. Red blood cells in abnormal amounts appeared sporadically in 4 cases; white cells were noted in pathologic quantities in 17 cases. As these patients were not always studied from a renal viewpoint, blood urea nitrogen, urea clearance and phenolsulphonaphthalein excretion determinations were few. One of those that died had a rising blood urea nitrogen, values of 43 mg.% 4 days before and 54 mg.% 2 days before death. The recorded causes of death of the other 4 were "liver shock," myocardial failure and hemorrhage, but a review of the records is not convincing that these were the causes of death. There was no notable difference in the urinary findings before and after operation.

In order to attack the problem from another angle, a study was made of cases dying of hepatic or biliary tract disease. Included in this study are all the patients who died between 1922 and present date of hepatic or biliary disease on the services of Dr. Müller and Dr. Ravdin, a total of 61 cases. Nearly all of these cases are known definitely to have been jaundiced. Operations were performed on 50 patients; autopsies, with complete study of the kidney, on 20. Chronic calculous cholecystitis and common duct obstruction was the diagnosis in 28 cases; the next most common condition was carcinoma of the head of the pancreas (9 cases); there were 6 cases of non-calculous common duct obstruction; 7 of cirrhosis of the liver; 2 of carcinoma of the gall bladder; and 1 case each of traumatic

rupture of the liver, acute hepatitis, carcinoma of the common duct, liver degeneration and necrosis of unknown etiology, carcinoma of transverse colon, retroperitoneal sarcoma, carcinoma of the liver (unverified), hepatic failure with septicemia and carcinoma of the stomach.

Low specific gravity of the urine was found in approximately the same percentage as in the first group. Of the 61 patients, 13 had a consistent specific gravity of 1.015 or less, and 30 had a specific gravity of 1.020 or less. Albumin, a trace or more, was seen in 55 cases; 27 cases showed a moderate or greater amount. This strengthens our impression that absence of albuminuria is not a distinguishing character of the renal changes associated with biliary or hepatic dysfunction.

TABLE 1.—INCIDENCE OF URINARY FINDINGS IN THE CLINICAL CASES STUDIED.

Series.	No. of patients.	Specific gravity.		Albumin.		Casts.		R.B.C.		W.B.C.		B.U.N.
		Below 1.015.	Below 1.020.	Pres.	Mod. or more.	Pres.	Many.	Pres.	Many.	Pres.	Many.	40-159 mg. %.
I	32	6	16	32	17	13	5	6	4	17	10	
II	61	13	30	55	27	44	27	24	8	57	21	10

Casts were seen in the urine of 44 patients; of these, 27 showed casts regularly and in large amounts. Twenty-four patients showed some red blood cells in the urine, and 8 of these had erythrocytes in large amounts. As in the first group of patients studied, there was an insufficiency of tests of renal function. However, on 11 patients upon whom phenolsulphonephthalein tests were made, the excretion was normal. The blood urea nitrogen was high in 10 patients, ranging from 40 to 159 mg. %. In 18 others, upon whom the determination was made, the range was between 8 and 27 mg. %. Although the clinical diagnosis of uremia was considered in only 4 of these patients, we cannot help but feel that the renal injury was a factor in the morbidity and mortality of more than 4 cases.

In practically all instances in which patients were discharged as improved, the excretion of albumin and casts cleared up before the patient left the hospital. The same is true of the excretion of red and white blood cells. In the series of patients who died, however, the urinary abnormalities continued until death (Table 2). Tubular degeneration was seen in all but 2 cases. In nearly half the cases (9) there was fibrosis or hyalinization of glomeruli. Localized areas of round cell infiltration were noted in 4 cases, 2 of these being in proximity to damaged glomeruli. Thirteen cases exhibited sclerotic changes in the small and large blood-vessels of the kidney.

**Experimental Studies.** We have investigated the pathologic changes in the kidney following experimental obstruction of the

common duct of 6 dogs. Using ether anesthesia, the common duct of each of these animals was doubly ligated and divided. A biopsy was taken from one kidney for control purposes.

So far 3 dogs have died during observations (Table 3) and 2 have been sacrificed. The lengths of life postoperatively were 22, 44, 42, 68 and 97 days. It is interesting to note that 4 of these 5 had perforated duodenal ulcers. Urinalyses and tests of phenolsulphonephthalein excretion were made at intervals. Some authors have reported a rise in phenolsulphonephthalein excretion in biliary obstruction while others have found no change.<sup>1,9</sup>

TABLE 2.—RENAL CHANGES IN THE 20 CASES IN SERIES II THAT CAME TO AUTOPSY.

Patient.	Tubular change.	Glomerular change.	Interstitial nephritis.	Blood-vessels.
A. R.	None	Hyalinization; thickened capsules	Subcortical	
A. C.	Cloudy, swelling	Fibrosis	Periglomer.	Fibrosis—retention cysts
M. R.	Epith. irreg., granular cells swollen	None	None	Engorged
S. B.	Swollen, granular, desquam.	None	None	Large arteries and arterioles thickened
J. S.	Swollen, granular	Number reduced	None	Few fibrosis scars
N. A.	Swollen, granular	None	None	Sclerotic (many cysts with and without hemorrhage)
I. K.	Granular	Hyalinization, fibrosis	None	Intimal thickening
E. K.	Flat, poorly preserved	Contain amorph. ppt.	None	None
F. H.	Vacuolated; am. masses of yellowish pigment	None	None	None
J. McC.	Marked cloudy swelling	None	None	Engorged
J. B.	Degen., desquam.	Thickened, gran., cap. loops in several	None	Large arteries, thickened
A. G.	Irreg. epithelium	Contain pink-staining material		
P. S.	Swollen, granular	Shrunken, fibrosis	None	Thickening of afferent arterioles; intimal change in small arteries
N. M.	Sl. cloudy swelling	None	None	Rare mesial arteriolar thickening
N. F.	Sl. degeneration	Mod. hyalinization	None	Some hyalinization of arterioles
J. U.	Swollen, irreg., granular	Occ. hyalinized	None	None
J. C.	Irreg., fat change, swollen	Hyalinization; areas of interst. nephritis	Occ. subcapsular	Thickening, hyalinization of small arterioles
O. S.	None	Obliterated in places by wedge-shaped scars	Infiltr. about glomeruli	Medial sclerosis of large vessels
R. P.	Swollen, granular; hyaline change	Fibrosis	None	Thickened with hyalinization in small arterioles (few)
R. McN.	Necrotic, disintegrating	Less cellular than normal; occ. scar glomerulus	None	Arterioles mod. sclerotic.

The 6 dogs all showed albumin in the urine after operation; all but 1 showed white blood cells and only 2 showed red blood cells in the urine. Casts were absent in all cases. Bile-stained renal cells, a condition thought by some<sup>8</sup> to be indicative of renal damage in obstructive jaundice, were noted in the urine of 3 animals. Thus the urinary picture of these animals was not as severe as in the clinical cases.

The method of determining the phenolsulphonephthalein excretion was as follows: The animals were catheterized and the bladder emptied. One cubic centimeter of phenolsulphonephthalein (6 mg.

TABLE 3.—PHENOLSULPHONEPHTHALEIN EXCRETION OF DOGS FOLLOWING EXPERIMENTAL OBSTRUCTION OF THE COMMON DUCT.

Dog 277.		Dog 341.		Dog 380.		Dog 496.		Dog 644.	
Date.	PSP, %.	Date.	PSP, %.	Date.	PSP, %.	Date.	PSP, %.	Date.	PSP, %.
1-6	Operation	1-13	Operation	1-25	90	2-15	55	3-18	55
1-25	70	2-6	60	1-27	Operation	2-17	60	3-20	55
2-10	55	2-20	70	2-8	70	2-17	Operation	3-22	Operation
3-8	75	2-24	Death	3-8	75	3-8	55	4-1	60
3-15	70	..	...	3-9	55	3-15	45	4-5	70
3-16	70	..	...	3-10	70	3-17	35	..	Death
3-17	70	..	...	3-15	60	3-20	60		
3-21	70	..	...	3-17	55	3-21	60		
4-3	70	..	...	3-20	60	3-22	60		
4-6	55	..	...	3-21	45	3-24	65		
4-8	55	..	...	3-22	35	4-3	60		
4-14	Death	..	...	3-24	70	4-6	60		
				3-27	60	..	Sacrificed		
				4-1	70				
				4-5	Sacrificed				

per cc.) was injected intravenously. Tap water (500 cc.) was given by stomach tube. At the end of an hour, the bladder was emptied (the catheter having been kept in place) and washed out with 60 cc. of tap water. The percentage of dye excretion was determined by comparison with a Dunning colorimeter (Table 3). It can be seen that there were no consistently striking depressions of the phenolsulphonephthalein elimination, although in 2 animals there was a depression with return to normal.

In 2 dogs (380 and 496) the phenolsulphonephthalein excreted was but 35%. In Dog 644 there is a slight rise in the phenolsulphonephthalein excretion following operation.

**Pathologic Findings.** In the sections of kidney obtained at autopsy there was no significant change found in the glomeruli. The blood-vessels and interstitial tissue were also normal. The main change was in the tubules, which were dilated and which showed compression of the lining epithelium. There were areas of vacuolization, fragmentation and desquamation in the tubular epithelium. Occasional casts were seen in the tubules; in the cells, in some instances, was seen a deposition of yellowish-brown pigment. These changes are essentially the same as those previously described in human "cholemic nephrosis."

**Summary.** Our clinical and experimental studies strongly confirm Elsom's<sup>6</sup> observations on renal changes in hepatic disease, except that our patients had a high incidence of albuminuria and a number of high blood urea nitrogen figures were noted.

A preëxisting renal lesion is intensified by a secondary "cholemic nephrosis." The high incidence of glomerular changes in the



patients that died suggests that a preëxisting renal lesion may have been present. This is strongly suggested by the fact that these changes predominated in the elderly patients.

If no previous renal injury exists, the evidences of "cholemic nephrosis" disappear rapidly following release of the obstruction. The major injury in this disorder is confined to the tubules.

The nephrosis associated with bile duct obstruction may be a determining factor in the final outcome and should not be looked upon as an inconsequential complication.

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### TUBERCULOSIS OF THE NASOPHARYNX.

#### POSITIVE SPUTUM WITH A ROENTGENOGRAPHICALLY NEGATIVE CHEST.

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SINCE Koch's<sup>4</sup> classic demonstration of tubercle bacilli in the sputum and Munier's<sup>7</sup> demonstration of their presence in the gastric contents, either finding has been considered indicative of a tuberculous lesion in the pulmonary parenchyma. During more recent years, attention has been called to the fact that tubercle bacilli found in the sputum may arise from lesions of the tracheobronchial tree. In the past 2 years, we have had occasion to observe 2 cases which suggest to us that still another source of tubercle bacilli in

the sputum should receive more serious clinical study. Both of these had tuberculous lesions of the nasopharynx; both raised their sputum in the characteristic manner for postnasal discharge; in both the sputum contained readily demonstrable tubercle bacilli; and in one, frequent roentgenograms of the chest and a bronchoscopic examination were negative for evidence of tuberculosis.

The following reports in the literature emphasize the need for further separation of the several possible sources of tubercle bacilli in the sputum and gastric contents when a pulmonary lesion cannot be demonstrated.

Steidl and Heise,<sup>15</sup> in 1931, in discussing the value of old tuberculin administered subcutaneously for diagnosis in 419 cases of "suspected pulmonary tuberculosis," found that 35 had a history of tubercle bacilli in their sputum before admission to Trudeau Sanatorium or that tubercle bacilli were found during their residency there. Later in 1934, Sampson and Brown,<sup>13</sup> reporting from the same place, state, "Another study of 312 patients without definite roentgenological change presenting one or more of the other four cardinal diagnostic criteria, revealed that 59 were said to have had tubercle bacilli in the sputum at some time, often before admission. . . ." In a recent personal communication with one of the authors<sup>12</sup> it is now roughly estimated that this number approaches the 100 mark. Some of these cases later developed roentgenographic signs of pulmonary tuberculosis; in others, giving a history of having had tubercle bacilli in their sputum, this may have been an erroneous observation; in still others, the focus of tuberculosis in the respiratory tract may have been in the nasopharynx, the trachea, or the bronchi.

Meersseman,<sup>6</sup> in June of 1938, reported from France a group of people he called "healthy expectorators" of tubercle bacilli. He apparently became interested in this problem in 1930 when he discovered a medical student and a young soldier with tubercle bacilli in their sputum and with negative chest x-ray findings. These 2 patients were not proved to be carriers of tubercle bacilli by guinea pig inoculation but the morphology and staining were so typical that the author did not doubt their being tubercle bacilli. Later, among 84 healthy medical students who were radiographically negative, he found one whose sputum produced a tuberculous death in a guinea pig 4 months after inoculation. In 1934, he examined 51 medical students with negative chest x-rays and 69 soldiers with negative fluoroscopic examinations. The sputum of each of these students and soldiers was inoculated into guinea pigs. Two medical students with negative chest x-rays had tubercle bacilli in the sputum and no x-ray changes developed over a 3-year period of observation. A third, a soldier, was found to have tubercle bacilli in the sputum by guinea pig inoculation and the chest x-ray taken after this finding was negative. There was no

x-ray follow-up of this case, but he withstood 1 year of military duty in apparent good health. The fourth case, a soldier, harbored tubercle bacilli in the sputum and the chest x-rays remained negative over a period of 1 year. In addition to his own cases, he cites the work of several French and one Spanish author who reported approximately 20 similar cases. Meersseman appears to have attempted to rule out any local source of tubercle bacilli by stating that at the time of the laryngeal examination he looked for any lesion capable of producing a positive sputum; but he makes no specific mention of having examined the nasopharynx. As an explanation of the above findings, he admits that the pulmonary lesion may exist but be too small to give x-ray change or clinical suggestion, but he prefers the theory that it is an elimination of bacilli by a healthy pulmonary parenchyma without concomitant or consecutive tuberculous evolution.

There are numerous reports of the finding of tubercle bacilli in the gastric contents, stools, or sputa of children with no demonstrable pulmonary tuberculosis. Most of these are concerned with tuberculosis of the hilar glands but some refer to cases with no roentgenographic evidence of intrathoracic tuberculosis, some with tuberculous cervical adenitis, others with tuberculosis of bone or joint. In 1927<sup>1a</sup> and again in 1931<sup>1b</sup> Armand-Delille, reporting on the guinea pig inoculation of gastric contents, found that some of the positive cases occurred in children (number not stated) presenting no clinical or roentgenographic evidence of pulmonary disease. Opitz, in 1930<sup>9a</sup> and in 1931,<sup>9b</sup> also reported the results of guinea pig inoculations of gastric contents. Among those in whom tubercle bacilli were discovered, he found 10 patients with negative chest x-rays, 8 having tuberculosis of the bone or joints, and 2 having a tuberculous cervical adenitis. Opitz, like Meersseman, mentions many similar cases seen by other physicians. Wallgren<sup>16</sup> reports a like study which yielded a few positive cases apparently lacking roentgenographic evidence of intrathoracic disease. Of the 24 positive culture or guinea pig inoculations of the gastric contents of children reported by Nalbant<sup>8</sup> in 1934, 4 were stated to have no x-ray change in the thorax.

It is apparent that the literature is fairly replete with instances in which the presence of tubercle bacilli in the sputum or gastric contents demands an explanation as to the site of their origin. Meersseman<sup>6</sup> apparently searched the lower pharynx and larynx as is common practice. Poulsen<sup>11</sup> refers to the tonsils as a possibility. Kereszturi *et al.*<sup>3</sup> suggest the possibility of a nasopharyngeal source, but no actual demonstration of such an origin is contained in the reports reviewed. We therefore wish to present 2 cases in which such demonstration has been made.

**Case Abstracts.** CASE 1.—S. K., a white Polish girl, of 18 years, was admitted to the University of Michigan Hospital, June 10, 1936, with the

history of severe colds and sore throats the preceding winter, and having noticed enlargement of the cervical glands 5 weeks before admission. The past history is of importance only in that the tonsils had been removed here 2 years previously and the pathologic sections failed to show evidence of tuberculosis.

Upon examination, the girl was found to be healthy except for the finding of bilateral cervical glands, several being enlarged to the size of a walnut and lying chiefly in the postcervical region. Admission laboratory examination showed only a slight lymphocytosis and a moderately elevated sedimentation rate.

*Course in the hospital:* The patient was admitted to the general medical service and there a biopsy of one of the cervical glands showed active caseating tuberculosis, after which the patient was transferred to the Tuberculosis Unit for observation and treatment. The routine examination of the concentrated sputum was reported as showing acid-fast organisms typical of tubercle bacilli. This finding was substantiated on four different occasions during the next 4 months. A stereoscopic x-ray examination of the chest was negative as was a similar study performed on the former admission 3 years before. While a patient on the Tuberculosis Unit, 4 monthly stereoscopic x-ray studies of the chest continued to show no evidence of tuberculosis. In view of the unexplained presence of tubercle bacilli in the sputum, oblique, lateral, apical detail, and Potter-Bucky x-ray studies were made and these disclosed no lesion of the lungs, pleura, or mediastinum. Bronchoscopic examination showed no evidence of tuberculous tracheobronchitis as a possible source of positive sputum. Following this period of 4 months' observation, it was decided to transfer this patient to a neighboring sanatorium for further observation. Just before her scheduled departure, in discussing the situation with the patient, we were for the first time impressed with the history of postnasal discharge and the absence of cough. Though we were not aware of a nasopharyngeal lesion as a sole source of tubercle bacilli in the sputum, the localization of the symptoms led us to ask the otolaryngologists to examine this area to see if such existed. They observed a white exudate in the adenoid area, and a smear from this readily showed acid-fast organisms typical of tubercle bacilli by direct examination. The adenoid tissue was removed by the LaForce adenotome and the pathologic report on this tissue was as follows: "Numerous epithelioid tubercles throughout the specimen of adenoid. Some with caseation necrosis." Smears and cultures from that area taken 6 days later showed no tubercle bacilli and nasal washings taken 9 days postoperatively were likewise negative for concentration examination and culture.

This patient has returned for examinations at 6-month intervals since discharge, the last visit being 26 months postoperatively. The postnasal secretion had so diminished after operation and up to the present time that she found difficulty in producing sputum, and that which was produced was negative on three concentrate examinations 2, 18 and 26 months postoperative, and on two cultures, 2 and 26 months postoperative. The severe sore throats she had experienced before operation had entirely disappeared. Roentgenographic examinations of the chest remained negative 26 months postoperative. The cervical glands responded promptly to the first period of bed rest and x-ray therapy, and at the last observation could not be palpated.

CASE 2.—A white male, aged 28, was admitted to the University of Michigan Hospital, March 3, 1938. He had been in good health until 9 months before admission when he noticed the sudden onset of pain in the mid-chest, dry cough and temperature elevation to 102°. The chest discomfort, which had been accentuated by respiration, lasted only 1 week,

but the temperature elevation to  $101^{\circ}$  persisted daily for 4 to 5 months. During this period, he had several x-ray examinations of the chest and a bronchogram performed in other hospitals without positive findings. Four months before admission to this hospital, and 4 to 5 months after the onset, he visited a large clinic where a diagnosis of Hodgkin's disease was made on the following findings: 1, x-ray at that time showed an enlargement of the upper mediastinum; 2, the cervical, axillary and inguinal nodes had also become enlarged; 3, the appearance of mild abdominal pain and abnormal resistance and tenderness on palpation of the abdomen suggested retroperitoneal adenopathy; 4, the patient reported decrease in the size of the glands and general improvement following the 11 x-ray treatments given there; 5, biopsy of a cervical gland was reported as follows: "Lymphnode showing diffuse changes of Hodgkin's disease. Areas of caseation necrosis but no tubercles." This quoted report was made by our pathologist who reviewed the slide after the tuberculous complication had been discovered here.

On admission here, the patient appeared acutely ill with evidence of long-standing illness. The temperature was  $100^{\circ}$ , pulse 100, respirations 24. There was a biopsy scar in the right supraclavicular fossa. There were multiple pea- to bean-sized anterior and posterior cervical lymph glands, and bilateral olive-sized axillary and inguinal lymph glands which were firm, discrete and non-tender. The chest examination suggested slight increase in the retromanubrial dullness.

The laboratory findings indicated a secondary anemia with suggestive evidence of a lymphoblastoma in the blood smear. Two concentrate examinations and a culture of the sputum were positive for tubercle bacilli as well as three direct smears.

The admission stereoscopic x-ray examination of the chest showed a fine stippling over the upper two-thirds of both lungs, which did not have the appearance of tuberculosis and was reported as being strongly suggestive of Hodgkin's disease of the lung parenchyma. There also was enlargement of the hilar shadows. Following our review of the chest x-rays, we were unwilling to accept the chest as a source of the tubercle bacilli in the sputum. The only tuberculous lesion it suggested was a localized miliary one, and if so, it was highly atypical in distribution, and, further, it is not our experience to expect bacilliferous sputum in such cases.

With the experience of the first case in mind, reinvestigation of this patient readily revealed the history of a profuse postnasal discharge which had been present for about 3 months. The laryngologist reported a small ulcer of the larynx and more importantly, an ulceration in the adenoid area about 17 mm. in diameter. A biopsy of the tissue in that area is reported as follows: "Numerous discrete and confluent epithelioid tubercles with caseation necrosis scattered throughout the tissue submitted. Small localized ulceration of the nasopharyngeal mucosa. Lymphoid hyperplasia. No evidence of Hodgkin's disease." Stain of the tissue readily showed acid-fast bacilli. The patient's course was rapidly downhill with daily temperature elevations to  $102^{\circ}$  to  $103^{\circ}$ . A week before death he developed intestinal obstruction, but in view of the prognosis and the patient's poor general condition, an operation was not performed. He died 22 days after admission. An autopsy was refused.

**Comment.** Two cases are cited to show that tuberculosis of the nasopharynx is a source of tubercle bacilli in the expectoration. In the first case, this was the only source discovered, and surgical removal of the focus relieved the patient of the symptoms and the infectious sputum, and more importantly, removed the necessity

for further treatment or isolation. The second case is cited mainly to support the fact that this area is a source of bacilliferous sputum and to call attention to the fact that whenever tubercle bacilli in the sputum tend to refute the clinical and roentgenologic diagnosis of a non-tuberculous condition, the nasopharynx should be investigated.

Both patients reported that the sputum was not brought up from the lungs by cough. In the first patient, the posterior cervical glands were shown by biopsy to be tuberculous. Since this chain drains the posterior nasopharyngeal area, it is believed that the adenoid lesion was a source of the tuberculous adenitis. The presence of these conditions, *i. e.*, postnasal discharge and posterior cervical adenitis should further direct attention toward the posterior nasopharynx in patients with a positive sputum from an unidentified source.

When the case records of the same material reported by Weller,<sup>17</sup> later by Magee,<sup>5</sup> and more recently by Pollard and Combs<sup>10</sup> were reviewed, it was found that enlargement of the posterior cervical lymph glands was not an invariable concomitant of tuberculosis of the adenoids.

It has been pointed out that the combination of a positive sputum and negative chest x-ray is not a rarity in the literature. It is not maintained that nasopharyngeal infection may account for all or even a majority of these instances, but it is shown that it may account for some. The incidence of tuberculosis in the adenoid tissue has not been studied as thoroughly as that of the tonsil. In 1917, Crowe *et al.*<sup>2</sup> showed by microscopic examination that 1.7% of the adenoids removed during 1000 routine tonsillectomies and adenoidectomies were tuberculous. Scarff and Whitby,<sup>14</sup> in 1929, inoculated guinea pigs with macerated adenoid tissue from 50 patients having routine adenoidectomies and, in 2 of these, positive results were found. It is interesting that these were the only 2 patients in the group with a tuberculous cervical adenitis.

It is not believed that the failure to consider this lesion will be a common source of error in clinical work but since the suspected area is accessible to the examiner by inversion of the laryngeal mirror, it is suggested that it be made routine in all cases of tuberculosis, and that it certainly never should be omitted in patients with postnasal drip and cervical adenitis. The examination should precede the bronchoscopic search for source of bacilli when the lung appears to be free of tuberculosis or to be adequately controlled by collapse therapy.

**Conclusion.** Two cases are presented to demonstrate that tubercle bacilli in the sputum may arise from the posterior nasopharynx; in 1 of these, this appeared to be the sole source of bacilli.

When the chest roentgenogram shows no evidence of tuberculosis, or when the changes present do not serve as a satisfactory explana-

tion as to the source of tubercle bacilli in the sputum or gastric contents, a tuberculous lesion in the posterior nasopharynx as well as one in the tracheobronchial tree should be suspected as the site of origin of the bacilli.

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## HEMORRHAGIC DIATHESIS WITH PROLONGED COAGULATION TIME ASSOCIATED WITH A CIRCULATING ANTICOAGULANT.\*

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THE possibility that hemorrhagic diatheses which are associated with a prolonged venous blood coagulation time may be due to the existence of a circulating anticoagulant has been suggested on several occasions.<sup>13,29</sup> However, as far as can be ascertained from the literature the presence of such an anticoagulant has never been actually observed in the plasma of a patient. Indeed in true hemophilia this hypothesis has been investigated and found to be untenable.<sup>26</sup> The purpose of this communication is to report the history, necropsy findings and certain investigations on a patient with hemorrhagic diathesis in whom a prolonged coagulation time appeared to be associated with the presence of a circulating anticoagulant.

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**Case Report.** *A 61-year-old mulatto male with 8 months cachexia, recent hemorrhagic manifestations, generalized lymphadenopathy and prolonged coagulation time, died of postoperative hemorrhage following excision of lymph node.*

**Present Illness.** J. S. (No. 922309, B. C. H.), a 61-year-old colored married American dining car waiter was admitted on December 6, 1938, complaining of pain in the left flank and left upper quadrant of 3 days' duration. This was cramplike but dull in nature and associated with febrile and chilly sensations. On the day before admission he vomited twice and had a severe epistaxis. For 8 months he had not been feeling well, suffering from dyspnea on exertion, mild orthopnea and ankle edema. During the 7 months prior to admission, after being unable to work for 6 months, he was digitalized and worked for the 1 month without distress.

**Family History.** Father died of "cancer of rectum." One sibling is thought to have died of tuberculosis many years ago. There was no history of hemorrhagic disorders.

**Past History.** Until the present illness the patient was remarkably well, working faithfully as a dining car waiter. During the last 7 years he suffered very slight epistaxes about once a year and had a hacking nocturnal cough. Thirty years ago he had gonorrhea and 6 years ago following a routine blood test he was given a few intramuscular injections the nature of which was not discovered but which produced a transitory attack of jaundice. There was no history of alcoholism or use of tobacco. In his occupation he was exposed to brass and silver polish and the usual fumes and smoke of the railroads. During the last year his weight fell from 75 to 64 kg. He was married twice. One daughter by his first wife is living and well.

**Physical Examination.** On admission he was acutely ill, fairly well developed, somewhat undernourished and moderately dyspneic. Temperature 39° C., pulse 100, respirations 24. Blood pressure 135/70. There were diminished resonance and moist râles at both lung bases. The heart was slightly enlarged to the left by percussion, with a gallop rhythm and precordial systolic murmur. The abdomen was tender in the left flank as was the left costo-vertebral angle. A small firm lymph node was palpable in the right supraclavicular space and both inguinal chains were moderately enlarged, the nodes being firm but freely movable.

**Laboratory Findings.** (A large amount of laboratory work was done on this patient and all duplicate findings are omitted.)

**Urine.** Microscopic hematuria and slight albuminuria were present constantly. The highest specific gravity of the urine was 1.026. On admission ureteral catheterization revealed that red cells were coming from left kidney.

**Blood (Hematology).** On admission the patient's hemoglobin was 75% (Sahli) (11.39 gm.), the red blood cell count 4.1 million, the white blood cell count 11,200; with 60% neutrophils, 24% lymphocytes and 16% monocytes. The patient's hemoglobin steadily declined, the only known blood loss being from hematuria and hematoma; on the 18th hospital day the hemoglobin was 36% (5.62 gm.). At this time the white count was 7900 with 65.5% adult neutrophils, 7.5% "bands," 3.5% eosinophils, 8.5% lymphocytes, 15% monocytes. There were no significant changes in these findings except for those transitory increases produced by transfusion and iron therapy. The mean corpuscular volume of the red cells averaged 90.0; the reticulocyte percentage 1.5. The corrected sedimentation rate (Rourke-Ernstene method) for whole oxalated blood was 1.2 mm./min. and for defibrinated blood 0.45 mm./min. Special hematologic findings are summarized in Table 1.

**Blood (Chemistry).** The non-protein nitrogen varied from 22 to 40 mg./100 ml. plasma. The total protein was 6.79 gm./100 ml. plasma and a partition of the protein showed the albumin to be 3.06 gm., the globulin 3.22 gm.



and the fibrin 505 mg./100 ml. of plasma. The fasting blood sugar and glucose tolerance curves were normal. The blood calcium was 8.74 mg./100 ml. serum, and inorganic phosphate 3.09 mg./100 ml. serum. The lipid constituents were essentially normal; total lipids 531 mg.; phospholipid 9.3 mg.; cholesterol 210 mg., free 81 mg. and ester 128 mg.; all per 100 ml. plasma. The blood cevitamic acid level was 0.55 mg./100 ml. plasma which while low is above the values found in scurvy. Takata Ara reaction ++++.

TABLE 1.—RÉSUMÉ OF LABORATORY FINDINGS PERTAINING TO HEMORRHAGIC DIATHESES.

Platelet count (direct)	335,000 to 937,000/c.mm.
Platelet morphology	Normal
Bleeding time (Duke)	$\frac{1}{2}$ to $3\frac{1}{2}$ minutes
Coagulation time (Patek and Stetson)	68 to 90 minutes
Clot retraction	Normal
Tourniquet test	Normal
"Prothrombin" time (Quick)	Normal
Serum calcium	8.74 mg./100 ml. serum
Plasma fibrinogen	505 mg./100 ml. plasma
Plasma vitamin C	0.55 mg./100 ml. plasma

*Miscellaneous.* The Hinton test on the blood serum was positive. No acid-fast bacilli were demonstrable in the sputum. The stools were positive on rare occasions for occult blood. Phenolsulphonaphthalein test showed 60% excretion of the dye in 2 hours following its intravenous injection. Blood group O (Moss IV). Hippuric acid excretion following sodium benzoate ingestion was 50% of normal on one occasion, normal at a later period.

*Roentgen Ray Findings.* Congestive changes were apparent in both lung bases and there was marked enlargement of the hilar glands. There was a hypertensive deformity of heart and the aortic knob was sclerotic. Both intravenous and retrograde pyelography were negative. Dilatable constrictions of third portion of duodenum and several other areas along small intestine and large intestine suggested pathologic changes extrinsic to gastrointestinal tract. The spine, humeri, skull and femora showed no abnormalities. There were calcified lymph nodes in the right groin.

*Clinical Course.* The admission symptoms subsided in 24 hours and at no time thereafter was there any recurrence of fever nor did the patient complain again of pain in left flank. Repeated physical examinations showed no noteworthy changes. He did fairly well on maintenance doses of digitalis until the 14th hospital day when he bumped his left hip against a table and developed a hematoma the size of a grapefruit. On his 23d hospital day he was transfused with 500 ml. citrated blood from a compatible donor without untoward reaction and was placed on ferrous sulphate 0.8 gm. daily. On his 33d hospital day he began to bleed moderately profusely from his right nostril. This hemorrhage was controlled by a pack impregnated with "steer globulin substance"<sup>30</sup> changed daily for 3 days when bleeding ceased. From this time on however the patient's condition gradually grew worse and he suffered two spontaneous hematomata in the left calf and right hip respectively. On the 64th hospital day because of the obscurity of diagnosis it was decided to biopsy the sternal bone marrow and to excise the right supraclavicular lymph node. There was no excessive bleeding at the time of operation, but postoperatively he bled from the supraclavicular incision into his neck and superior mediastinum, packing of the wound and a 500 ml. transfusion proving of no avail in stopping the hemorrhage and he died on his 66th hospital day.

*Biopsy of Sternal Bone Marrow and Supraclavicular Lymph Node.* The sternal bone marrow was essentially negative on gross and microscopic



FIG. 1.—Cut section of lymph nodes at bifurcation of trachea.



FIG. 2.—Cut section of lymph nodes surrounding duodenum.

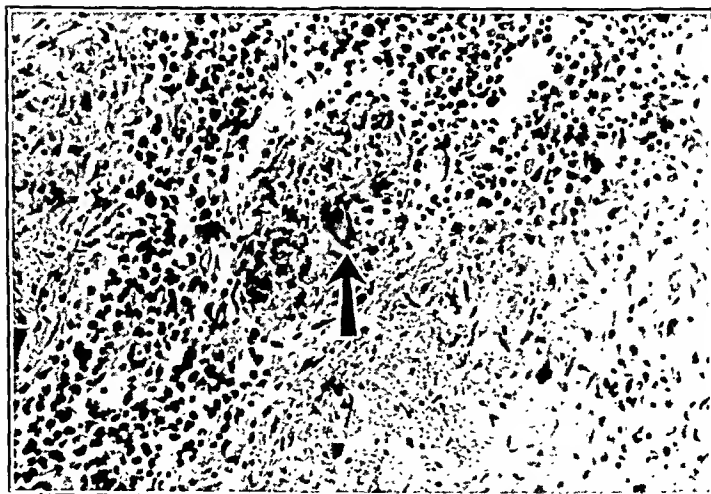


FIG. 3.—Small active tubercle from pancreatico-duodenal lymph node. ( $\times 186$ .) Note histiocytic center with Langhans giant cell (arrow) and surrounding lymphocytic reaction.

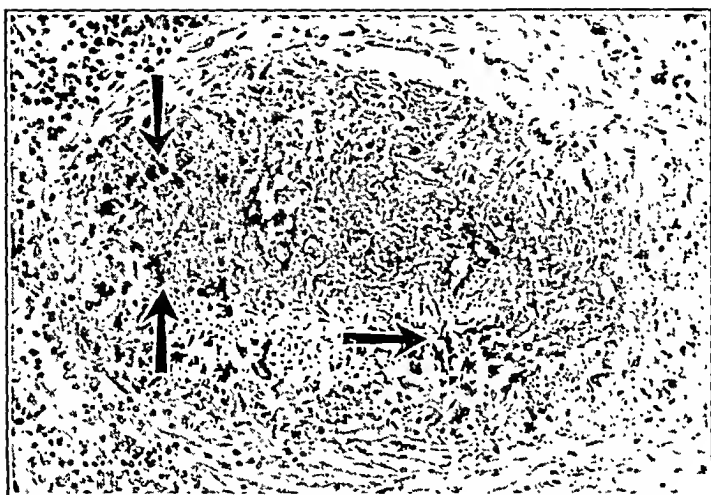


FIG. 4.—Small healed tubercle from pancreatico-duodenal lymph node. ( $\times 186$ .) Note hyalinized center of nodule containing pigment (arrows) and surrounded by fibrous tissue.

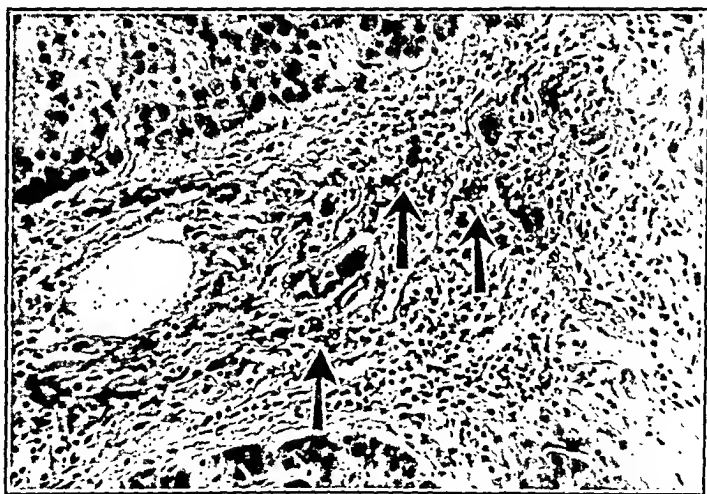


FIG. 5.—Portal space of liver. ( $\times 310$ .) Note deposits of pigment (arrows) in connective tissue.

examination. The supraclavicular lymph node was 1 by 1 by 2 cm. in size, firm in consistence and mottled dark gray and black in color on cut section. On microscopic examination, it showed marked anthracosis and fibrosis, and lesions with hyalinized centers surrounded by lymphocytic reaction suggesting healing tubercles. An acid-fast stain for tubercle bacilli revealed no such organisms. However, when a guinea pig was inoculated with some of the macerated tissue, it developed manifest tuberculosis.

*Necropsy* (performed 15 hours after death). The body length was 173 cm. and the weight 50.1 kg. There were fresh ecchymoses over the swollen neck extending on to the upper anterior chest. In the right supraclavicular fossa, there was a wound, 3.5 cm. in length, packed with blood-soaked gauze, and another over the midsternum, 4.5 cm. in length, which was sutured and apparently healing. There was no peripheral edema.

On opening the thorax, the anterior *mediastinum* showed dark purple hemorrhagic areas extending from the sternal notch to the superior border of the pericardium. Firm fibrous adhesions were found in both pleural spaces. In the pericardial cavity a few thin fibrous adhesions and 3 to 4 ml. of clotted blood were present. A small subepicardial hemorrhage was observed posteriorly. The *heart* and *lungs* appeared otherwise negative. The heart's blood was sterile on culture. In the pelvic region, the parietal and a portion of the visceral *peritoneum* was conspicuous by its dark gray almost black color. This was attributed to a previous retroperitoneal hemorrhage, the source of which, however, could not be located.

The *liver* was slightly increased in weight (1600 gm.) but otherwise presented no gross abnormalities. A single brown granular stone 2 cm. in diameter was found in the *gall bladder*. The *aorta* showed a mild degree of atheromatous change. The femoral *bone marrow* was a mottled mixture of dark red brown tissue and fat, the vertebral marrow was pale red brown and the tibial marrow was entirely fatty.

The most striking pathologic change to be found at autopsy was in the lymphatic system. Every lymph node that was available at postmortem examination was involved by a granulomatous lesion to a greater or less degree. The inguinal nodes were apparently most affected being grossly caseous and containing several areas of calcification. The tracheo-bronchial and hilar nodes in the chest and the pancreatico-duodenal, periportal and mesenteric nodes in the abdomen were all discretely enlarged varying from 0.5 to 5 cm. in diameter. The nodes in the chest were of rubbery consistence and cut with a cartilaginous gritty sensation. Those in the abdomen were slightly softer. All showed on cut section a speckled dark green and gray surface with the configurations of green granite. (See Figs. 1 and 2.)

The remainder of the organs were grossly negative.

*Microscopic.* The chief lesions were in the lymphatic system. Every node examined presented the histologic evidences of tuberculosis. The inguinal nodes were apparently most affected, being composed largely of caseous and calcareous deposits. The supraclavicular, tracheo-bronchial, hilar, pancreatico-duodenal, periportal and mesenteric nodes all contained focal areas of fibrosis and caseation necrosis (Fig. 4) with deposition of calcium and cholesterol. In selected regions of these nodes typical active tubercles could be demonstrated. These showed a histiocytic center with Langhans giant cells and surrounding lymphocytic reaction (Fig. 3). Stains for acid-fast bacilli however revealed no such organisms. In the remainder of the organs there were no lesions absolutely characteristic of tuberculosis. In the lungs there was a focal area of fibrosis which was consistent with a healed tubercle.

The amount and distribution of anthracosis in the tissues was greater than that usually seen. Carbon pigment was present in all the lymph nodes except those in the inguinal region. The lungs contained unusually large

amounts. Pigment with the appearance of carbon was also present in the connective tissue of the portal spaces of the liver (Fig. 5) and in the reticulo-endothelial cells of the spleen and vertebral bone marrow. There was slight periportal cirrhosis in the liver.

The tibial and vertebral bone marrow presented a moderate hyperplasia of both the erythropoietic and leukopoietic elements.

Both kidneys contained focal areas in which most of the tubules were replaced by fibrous connective tissue in which there were infiltrating lymphocytes. The tubules remaining in these areas contained darkly basophilic hyaline material in the lumens.

The sections were examined for silica with the polarizing microscope. In the lung nodule previously described and in the hilar and cervical lymph nodes, rare doubly refractile crystals consistent with the appearance of silica were found. The amount however was within normal limits and far below that seen in silicosis.

*Final Postmortem Diagnoses.* Generalized tuberculosis of lymph nodes. Anthracosis of lymph nodes, lungs, liver, spleen and bone marrow. Findings consistent with a hemorrhagic diathesis (hemorrhage from operative wound, old retroperitoneal hemorrhage, subepicardial hematoma and hemo-pericardium). Hyperplasia of bone marrow. Fibrous pleuritis, bilateral. Healed pyelonephritis, bilateral. Chronic cholecystitis and cholelithiasis. Slight biliary cirrhosis of liver.

Generalized lymph node tuberculosis is a rare condition. In this patient, as in most of the cases reported, the portal of entry of the organism is unknown. The subject has recently been reviewed by Miller.<sup>20</sup>

**Investigation of the Coagulation Defect of Patient's Blood.** The results of the routine laboratory tests are condensed in Table 1. The most striking abnormality was the prolonged blood coagulation time, ranging from 68 to 90 minutes on numerous occasions. This finding was clearly not associated with fibrinogen, prothrombin or calcium deficiency and the platelets were increased rather than diminished. The laboratory examinations resembled closely those presented by true hereditary hemophilia. There was, however, nothing in the patient's past or family history to suggest such a diagnosis.

Certain standard procedures developed during the past 3 years in this laboratory<sup>26,27</sup> for the study of the coagulation defect in hemophilia were applied to this patient. A transfusion of 500 ml. citrated blood from a normal compatible donor was given the patient but was followed by no change in the coagulation time of his blood. This is strikingly different from the fall in the coagulation time of patients with hemophilia produced by such transfusions of whole blood or plasma.<sup>23,26</sup> Using the standard technique previously described,<sup>26,27</sup> it was observed that the addition to 2 ml. of the patient's blood of various amounts of normal plasma\* and of

\* Hereafter the word plasma refers to the preparation obtained by adding sodium citrate to whole blood so that the final citrate concentration is 0.25%, centrifuging at 2000 r.p.m. for 30 minutes, filtration through No. 2 Whatman paper and then through a Berkefeld V filter.

certain derivatives of plasma known to reduce the coagulation time of hemophilic blood did *not* reduce the coagulation time of this patient's blood. It was found, however, that the addition of 0.4 ml. of an 0.5% solution of calcium chloride did reduce the clotting time of 2 ml. of the patient's blood from 68 to 27 minutes *in vitro*. Larger amounts of calcium chloride had no further effect.

When small amounts of the patient's plasma were added to 2 ml. of normal human blood the coagulation time of the normal blood was increased from 7 to 28 minutes in one instance and from 11 to 32 minutes in a second (Table 2). This anticoagulant effect of the

TABLE 2.—EFFECT OF CALCIUM ION, PATIENT'S AND HEMOPHILIC PLASMA ON THE COAGULATION TIME OF NORMAL BLOOD.

ML. of materials added to 2 ml. of normal blood.			Coagulation time of mixture in minutes.
Patient's plasma.	Hemophilic plasma.	0.5% calcium chloride.	
0	0	0 (control)	7
0.01	0	0	10
0.05	0	0	19
0.10	0	0	28
0.20	0	0	42
0.10	0	0.10	16
0.20	0	0.10	16
0	0.10	0	9
0	0.20	0	15
0	0.10	0.10	6
0	0.20	0.10	6
0	0	0.10	5

patient's plasma on normal blood was striking in dilutions of 1 to 20 and 1 to 40 and still quite apparent at a dilution of as great as 1 to 200. The addition of calcium chloride partially inhibited this anticoagulant effect as it partially reduced the clotting time of the patient's own blood. When these observations were repeated with hemophilic plasma on normal blood no anticoagulant effect of the hemophilic plasma could be demonstrated except in dilutions of 1 to 10 when the characteristic prolongation due to citrate ion intervened.

A preliminary\* investigation into the nature of the anticoagulant in this patient's plasma was attempted. The slightly increased plasma globulin and fibrinogen levels of this patient suggested the possibility of liver damage. Because of this the question arose as to whether this patient might have an excessive amount of heparin in the circulating blood. Chargaff<sup>5</sup> has shown that heparin when present in blood may be neutralized by the addition of salmine sulphate. When this patient's blood was titrated with this pro-

\* 200 ml. of this patient's blood plasma were obtained during life and were "lyophilized" and some of these observations were made postmortem on such plasma after rediluting to the original volume with distilled water.

tamine\* in amounts varying from 0.001 to 0.1 mg. per 2 ml. of blood there was *no* effect on the coagulation time except that with increasing concentration of salmine sulphate the intrinsic anticoagulant effect of this substance became manifest. On the basis of Chargaff's report the amount of salmine sulphate used in the above experiment should have served to neutralize concentrations of heparin varying from 100 to 10,000 inhibitor units per kg. body weight. We accepted these observations as evidence that the anticoagulant substance was not heparin.

The anticoagulant was relatively thermostable, resisting a temperature of 37.5° C. for 72 hours and 61° C. for 10 minutes. Ultrafiltrates of the patient's plasma through cellophane membranes under a positive pressure of 20 cm. of mercury for 24 hours contained no anticoagulant activity. This would indicate that the anticoagulant is not a simple diffusible substance.

Dialysis of the plasma against distilled water for 8 days at a temperature of 8° C. yielded an euglobulin fraction and a water-soluble protein fraction neither of which had anticoagulant action. Unlike preparations from normal plasma,<sup>18,27</sup> the euglobulin possessed no clot promoting activity for hemophilic blood. When the globulin fraction was prepared by diluting the plasma with 10 times its volume of distilled water and precipitation with 1% acetic acid at pH 5.6, it was found to be neither coagulant nor anticoagulant for hemophilic blood. Such preparations from normal plasma have marked clot accelerating power for hemophilic blood.<sup>27</sup> Removal of the proteins from the plasma by ethyl alcohol<sup>15</sup> left an alcohol residue which when evaporated to dryness *in vacuo* and redissolved in water showed *no* anticoagulant activity.

Continuous ethereal extraction for 24 hours employing a Soxhlet extractor did not yield an active extract but the residue retained its full anticoagulant activity.

No fibrinolysin was demonstrable in the patient's plasma or serum.

**Discussion.** The patient described represents an individual with hemorrhagic diathesis associated with a prolonged coagulation time. This finding is relatively uncommon and the conditions in which it occurs have recently been reviewed by Pickering.<sup>28</sup> In only true hemophilia is such decreased coagulability of the blood an invariable finding. The clinical and genetic characteristics of this disease are well described<sup>1,2</sup> but the pathologic physiology still remains incompletely understood.<sup>16c,27</sup> The individual reported here can be sharply differentiated from hemophilia on the basis of the obviously dissimilar clinical picture and certain established physiologic criteria. The latter include the failure of blood transfusion to reduce the coagulation time of the patient's blood *in vivo* and the failure of normal human plasma and certain of its active components to

\* Kindly furnished by Eli Lilly and Company, Indianapolis, Indiana.

reduce the coagulation time of the patient's blood *in vitro*. These same criteria also differentiate the patient reported here from the female patient of Joules and Macfarlane,<sup>17</sup> who presented a prolonged blood coagulation time which was reduced *in vitro* by the addition of normal human plasma. In certain other hemorrhagic diatheses, increased coagulation time has been reported occasionally. Among these are biliary obstruction, biliary fistula or liver disease.<sup>4</sup> The decreased coagulability of the blood in these conditions appears to be associated with a vitamin K deficiency and a consequent reduction of prothrombin in the blood.<sup>3,31</sup> Lack of fibrinogen may be responsible for prolongation of the clotting time. This is usually congenital<sup>19</sup> but may be associated with hepatic insufficiency.<sup>24</sup> In thrombocytopenia prolonged clotting time has been reported in surprisingly rare instances<sup>34</sup> in spite of the decreased coagulability said to accompany artificial removal of the platelets.<sup>7,8</sup> In 1915, Hess<sup>14</sup> reported a patient with hemophilia which he suggested was due to calcium deficiency on the bases of a negative calcium balance and of the shortening of the coagulation time of the patient's blood produced by the addition of calcium chloride *in vitro*. This condition he termed "hemophilia calcipriva." However, the patient was only 6 years old, at which age a negative calcium balance is not unusual and the direct effect of the addition of calcium has been repeatedly observed in true hemophilia.<sup>16a,18b</sup> In addition, it has been observed in the coagulation of dog's blood that levels of calcium sufficiently low to interfere with clotting were far below those compatible with life of the animal.<sup>32</sup> It is doubtful therefore that "hemophilia calcipriva" can exist. The patient reported here may be differentiated from all these conditions by the laboratory observations. The "prothrombin" time, icteric index, blood fibrinogen, serum calcium were all within normal limits. The blood platelet counts were somewhat elevated. In spite of a slightly elevated plasma globulin level, the liver function as tested by sodium benzoate detoxification was grossly normal.

At times there has been reported in connection with certain conditions a hemorrhagic diathesis with a prolonged coagulation time unassociated with prothrombin, fibrinogen or calcium deficiency. These include tertiary syphilis,<sup>25</sup> multiple myeloma<sup>10</sup> and uremia.<sup>9</sup> The patient reported here had a positive blood test for syphilis but at autopsy there was no anatomic evidence of this disease. Multiple myeloma was not present at autopsy and during life it was impossible to demonstrate Bence-Jones protein in the urine. Repeated blood non-protein nitrogen determinations were within normal limits.

In the consideration of the nomenclature of the condition which this patient presented, the term "pseudohemophilia" suggests itself. This is a term which has been applied to hemorrhagic diatheses associated with a prolonged coagulation time but equally



to those resulting from fibrinogen deficiency<sup>28</sup> and to those resembling hemophilia.<sup>19</sup> In addition, it has been very frequently applied to Glanzmann's hereditary hemorrhagic thrombasthenia,<sup>11,12,21,33</sup> a disorder characterized by normal or prolonged bleeding time and by normal clotting time. This term therefore is ambiguous and misleading.

In all probability the most significant laboratory finding to be related to the prolonged coagulation time of the patient reported here is the demonstration of the presence in his circulating blood of a substance interfering with the completion of the normal clotting mechanism.\* Whether this anticoagulant is identical with the "inhibiting substance" of Howell<sup>16a,b</sup> cannot be said. It does, however, possess the thermostability and non-diffusibility of that "substance."<sup>16a</sup> As far as the demonstration of the existence of some "inhibiting substance" is concerned, the data given in the text exhibit this situation even more comprehensively than the usual *in vitro* exposition<sup>16a,19</sup> of antithrombic activity since the inhibition of blood coagulation occurs *even when calcium, prothrombin and fibrinogen are present in adequate amounts in the system.*

The unusually generalized anthracosis extending even into the liver observed at postmortem examination appears to be the only anatomic finding which might bear a relationship to the pathologic physiology of this patient. What this relationship is can only be speculation at the present moment. As far as the generalized lymph node tuberculosis is concerned, a review of the literature has revealed that several cases presenting purpura hemorrhagica have been reported<sup>6</sup> but none in which the coagulation time is mentioned as being prolonged. Minot<sup>21</sup> has reported hemorrhagic diathesis with prolonged coagulation time in a patient with miliary tuberculosis.

To recapitulate then, the patient reported here was a 61-year-old mulatto dining-car waiter presenting an 8-month history of progressive cachexia. Physical examination revealed slight lymphadenopathy and the ordinary degenerative findings of his age group. The routine laboratory studies revealed serologic syphilis, microscopic hematuria, moderate hypochromic anemia, occasional melena and hematemesis and prolonged coagulation time. There was roentgenographic evidence of hilar enlargement in the chest and multiple lesions extrinsic to the gut in the peritoneal cavity. During his hospital course he developed 2 traumatic hematoma, 2 spontaneous hematoma, and a severe epistaxis. He died of postoperative hemorrhage following excision of a cervical lymph node and

\* Dr. W. H. Howell<sup>16d</sup> after kindly reviewing the data presented by this patient has pointed out that in addition to the presence of an anticoagulant a deficiency of "globulin substance"<sup>24</sup> or "plasma thromboplastin"<sup>16c</sup> may have contributed to the prolonged coagulation time.

biopsy of sternal bone marrow. The essential postmortem finding was generalized lymph node tuberculosis and anthracosis. The most interesting observation concerning the patient was the anticoagulant activity of his plasma for normal blood. The anticoagulant is a thermostabile, non-diffusible and non-ultrafilterable substance.

**Summary and Conclusions.** A patient with hemorrhagic diathesis is reported in whom a prolonged blood coagulation time was associated with the proven existence of an anticoagulant in his blood plasma. The postmortem examination revealed generalized lymph node tuberculosis and anthracosis. The relationship of these findings to the pathologic physiology involved is not established.

It is quite possible that the presence of a circulating anticoagulant may be associated with the prolongation of the blood coagulation time found in other conditions. It would seem advisable therefore that in such instances the anticoagulant properties of the patient's plasma should be investigated.

We appreciate the coöperation of Dr. Emmanuel Deutsch, Surgical Research Laboratory, Boston City Hospital, in performing the blood lipid and hippuric acid excretion determination, and of Dr. Stanley Nowak, Fifth Surgical Service (Harvard), Boston City Hospital, in numerous surgical consultations on this patient.

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## TRICHINOSIS.

## A STUDY OF 23 CASES.

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THE subject of trichinosis has recently attracted considerable attention. This interest has come for the most part from an effort of the United States Public Health Service to obtain data regarding the distribution of the parasite in the general population and from their desire to offer a program for the effective control of the disease. A general impression of the incidence of trichinosis may be obtained from the Annual Report of the Surgeon-General of the Public Health Service of the United States.<sup>2</sup> For example, an examination of 2000 diaphragms in and around Washington, D. C., showed that 17.1% were positive for trichinæ. In a series comprising material received from hospitals selected at random in various parts of the United States, 375 diaphragms were examined and 18.8% were found to be positive for trichinæ. It is interesting to note that of 98 diaphragms in a series of individuals who met death from accidents, 15.3% were positive for trichinæ. In order to determine the distribution of trichinosis throughout the country as a whole, sections of diaphragms were obtained from states in which the disease had never been reported. From Arizona 24 diaphragms showed an incidence of 12.5%; of 77 diaphragms from New Hampshire, 16.9% were affected; and an examination of 26 diaphragms from Oklahoma disclosed the trichinella in 26.9%. At the Milwaukee County Hospital 10 diaphragms were examined and the incidence was found to be 20%.

These studies leave no doubt that trichinosis is much more prevalent than it is usually thought to be. A general review of the work done on the subject shows that at postmortem examination about 1 individual in 6 has positive evidence of the disease. It may be concluded, then, that most patients who have had trichinosis either gave no clinical evidence of the disease or the signs and symptoms were misinterpreted and an erroneous diagnosis made. With a view of obtaining further data upon the question of trich-

inosis in this vicinity we have collected all the cases diagnosed clinically at this hospital for the past 8 years.

Reports such as those given by Aldridge<sup>1</sup> and Carlson<sup>7</sup> show that outbreaks of trichinosis occur in certain districts. In these epidemics the cases appear to show the classic characteristics more definitely than the sporadically collected cases. The series of cases reported here were diagnosed from 138,060 patients entering the hospital from January 1, 1931, to January 1, 1939. In many instances the diagnosis had been made before entrance, but in others the condition had been mistaken for some other disease.

The main clinical data of the series are included in Table 1. In the 23 cases presented here, the age incidence ranged from 17 to 57 years. Only 2 patients were 50 years old or over. This is in distinct contrast to Pote's<sup>27</sup> series. He reported that of 163 cases, 32.2% were in the age group of 15 to 50 years, while 61.9% were over 50 years. In our series, 12 of the patients were males and 11 were females; sex differences seemed to have no significance. The patients came from all walks of life; 2 were physicians, 1 a nurse, and most were laborers. Occupation had no importance, for a disregard of the danger of eating poorly prepared food does not characterize any particular class. In 14 cases there was a history of having eaten inadequately cooked pork, raw hamburger sandwiches or hamburgers obtained from stands along the roadside. A cursory glance at our table shows that most of the patients developed trichinosis during the warmer periods of the year when road-side stands are operated for the convenience of the motoring public.

Marked leukocytosis occurred in all but 2 cases (Cases 3 and 18). Both of these patients recovered. Eosinophilia was definitely established in all but 1 (Case 2), and this patient died. The maximum eosinophilia was 73% (Case 16) and the minimum 4% (Case 2). An autopsy done in the latter case established the diagnosis of trichinosis.

Trichinosis does not always present a uniform clinical picture. The forms showing the classic picture are recognized easily and promptly while in the unusual types, such as those in which essential internal organs are involved, diagnosis may be very difficult. Most of the cases reported here were of the common type and began with nausea, vomiting, abdominal distress and diarrhea which came on within several hours after having eaten the questionable meat. Occasionally these gastro-intestinal disturbances were lacking, and frequently they were attributed to some disorder entirely unconnected with trichinosis. Pain in the muscles and joints and swollen eyelids were by far the most outstanding clinical features noted. Fever was not marked in any case, and frequently it was completely absent. Of the 23 cases reviewed here, 7 had few symptoms, 6 had symptoms of a moderate degree of severity and in 10

the signs and symptoms were well developed and the patients were very sick. The conditions most commonly confused with trichinosis in this group of cases were sinus infection, influenza, rheumatic fever, la grippe and acute nephritis. In 3 cases a more serious diagnosis such as typhoid fever or tularemia was suspected. A diagnosis of acute nephritis was made before the true condition was recognized in 2 patients. The disease was identified in most cases when the high eosinophil count was found in association with the other features of trichinosis. When any doubt existed a muscle biopsy was done and the Bachman test was resorted to in a number of cases.

Most of the patients were free of symptoms after 2 or 3 weeks. However, the course was more prolonged in several of the more severe cases. In 1 case, thrombophlebitis of the left femoral vein developed and the patient was confined to the hospital for several months. Of the 23 cases, 2 died and 21 recovered completely, a mortality rate of 8.6%.

It did not appear to us that the treatment after entrance to the hospital had much influence upon the course of the disease. When the larvæ become encysted in the muscles or organs of the body very little can be accomplished in a specific way in treatment. We were impressed with the fact, however, that the individuals seen in the earlier stages by a physician who was thoughtful enough to clean out the gastro-intestinal tract had a milder course and recovered more promptly. Anthelmintic measures such as male-fern and santonin were employed in some of our cases without much effect. Copious amounts of fluid and a highly nutritious diet were given. Palliative measures such as sedatives and acetyl salicylic acid were used for the relief of pain and headache. In some cases intravenous injections of calcium gluconate, mercurochrome and gentian violet were employed, but the value of these therapeutic procedures seemed very doubtful to us. Fantus<sup>12</sup> recommends a preliminary purge with mercurous chloride (0.2 gm.) followed in 8 hours by a dose of magnesium sulphate. He repeats this treatment several days in succession in order to sweep out the worms that have not invaded the submucosa. Good results were reported by Grove<sup>14</sup> who used antimony and potassium tartrate in a 2% solution intravenously. Our clinical experience from the therapeutic standpoint coincides with the experimental work done by Miller, McCoy and Bradford<sup>25</sup> who tested the efficacy of many of these intravenous treatments experimentally. They concluded that no demonstrable therapeutic effect was obtained. On the basis of their work they questioned the rationale of intravenous injections of such substances as gentian violet, antimony, potassium tartrate, neoarsphenamine, metaphen and iodine.

**Discussion.** It is generally agreed that the high incidence of trichinosis observed at autopsy is not reflected clinically. As Pote<sup>27</sup>

aptly points out, a study of each of his 163 positive cases revealed that infestation did not seriously affect the health of the individual or the course of the terminal sickness. However, from our own series of cases and from a study of the literature there can be no doubt that in some instances trichinosis is a grave clinical condition that may cause weeks of disability or even death.

From the data published by Hall and Collins<sup>17</sup> it is apparent that measures used to control trichinosis during the past 50 years have failed. There is no microscopic inspection of pork in this country, and fresh pork or pork products to be eaten after cooking by the consumer are not processed. As pointed out by Hall the government inspects only about 70% of the meat sold. In packing houses operated under Federal supervision all pork products that are to be used without cooking are processed to kill the trichina, but about 50% of the pork goes to the consumer in raw state. Lack of proper processing is considered to be a fertile source of trichinosis, and another common cause is pork products prepared without supervision in small local slaughter houses or on farms. Since the United States government long ago gave up attempts to eliminate trichinosis by microscopic examination of pork, considerable meat has been marketed in this country without any inspection whatever. Fresh pork sausage, smoked hams and shoulders, bacon and such products as smoked sausage, boneless loins, and coppa should be cooked until they are well done throughout before consumption. Thirty minutes to the pound is an approximate guide to sufficient cooking for large, thick cuts of pork. Pork products of the sort customarily eaten without cooking by the consumer, largely various kinds of dry or summer sausage are entirely safe to eat without cooking if prepared under Federal or other competent inspection. The pork used in such products is especially processed by cooking, freezing or curing to destroy any trichinæ that may be present.

Until recent years no steps were taken to solve the problem of trichinosis, but the latest work of Hall and his associates seems to have laid a foundation for subsequent control. A summary of the problem may be taken from Hall's last report.<sup>16c</sup> Human trichinosis rests, he states, upon the basis of swine trichinosis and swine trichinosis rests primarily upon uncooked pork scraps in garbage, table scraps and swill, the rat having only a minor and not definitely ascertained rôle in swine trichinosis. He insists that the basic solution of the problem lies in keeping raw and inadequately cooked pork scraps out of the feed of swine. His suggestion for the control of trichinosis calls for improvement in methods of raising swine, these improvements to be specified by the packers as requirements to be met by swine growers before their products can be marketed. The elimination of the dangerous practice of feeding raw or inadequately cooked pork scraps to swine would play an important rôle in the control of trichinosis. He warns that useless publicity or ill-

advised legislation are not the correct control measures for trichinosis and that the packer and swine grower should be called upon to cooperate in the solution of the problem.

*Etiology.* The *trichinella spiralis*, the parasite which causes the disease, exists in an encysted form in the muscles of the rat, pig, wild boar, dog, fox, bear and badger. Lower animals are the normal hosts for the organisms; human infection is accidental. When a human being ingests trichinous meat, the cyst wall is digested in the stomach and the worms pass actively into the small intestine where they reach maturity in about 3 days. The females are fertilized, and on about the seventh day they burrow into the mucosa of the intestine, allowing embryos to escape into the tissues and lymph spaces. It is not definitely known how the embryos get from the intestinal wall to the muscles, but it is probable that they pass through the lung into the general circulation because of the fact that they are smaller than a red blood cell. By the tenth day the embryos are usually found in the muscles where they grow to maturity, often becoming as large as 1 mm. in length. They coil up and become completely encysted by the twelfth week and may live in this state for 20 or 30 years. When the meat containing these cysts is eaten the cycle is started again. There is little chance for further development once the embryos become encysted in the muscles of a human being. It is only among lower animals that the worms develop from generation to generation.

Infection with the *trichinella spiralis* is common in hogs throughout the world. Ransom<sup>28</sup> tabulated the results of the United States Government trichina inspection of over 8,000,000 hogs exported during 9 years between 1898 and 1906. Living trichinae were found in 1.41% and in addition 1.16% contained trichina-like bodies or disintegrating trichinae. In other words, 1 out of every 79 hogs was infected, or, if dead and trichina-like bodies are included, 1 out of every 39 hogs. Blumer<sup>6a</sup> states that 6% of American hogs have the disease, and Hall<sup>16b</sup> estimates the incidence at 1 to 2%. The parasite is most prevalent among garbage-fed hogs, between 4 and 5% being infected. The fallacy in the idea that, since Federal examination of millions of hogs showed a trichina incidence of only about 2%, the danger of infection is slight, is pointed out by Riley and Scheffley.<sup>30</sup> The average found in millions of examinations is not applicable to any given community since there might be practically no infected animals or almost any ratio might exist, depending on local or temporary conditions.

*Course and Diagnosis.* Unlike many infectious diseases, the amount of infected material ingested determines the severity of the symptoms in trichinosis. If the meat is only slightly infested, large quantities must be eaten to produce ill effects, and the meat must be heavily infected if severe trichinosis is to follow the ingestion of small amounts. This fact was first pointed out by Ransom.<sup>28</sup>

A note written on December 22, 1897, by Osler on a case of trichinosis in the Johns Hopkins Hospital, reported by Thayer,<sup>34</sup> describes the classic picture: "The face and eyelids are puffy, the face suffused and red, the tongue clean, the arms and hands much suffused—the latter being cyanotic, they are closed with difficulty as they are so stiff. The feet and arms are considerably swollen, particularly over the backs and wrists where they are puffy. The swelling of the arms is actually in the muscles which are sore; there is distinct soreness of the trunk. The feet are livid, the legs still and cold, the muscles of the calves are not particularly swollen, not very tender."

According to Ransom,<sup>28</sup> trichinosis is difficult to diagnose and an important characteristic of the disease, whether mild or severe, is the lack of regularity in its course. Hall<sup>16a</sup> states that no adequate clinical picture of trichinosis is available and that the effects produced by the worm will be conditioned by the following factors: 1, the number of worms present; 2, the size of the patient; 3, the tissues invaded; and 4, the physical condition, resistance and concomitant pathologic conditions in the individual attacked by the parasite. When considered from this point of view trichinosis becomes a highly complicated and little studied disease. The onset varies considerably as pointed out by Blumer.<sup>6b</sup> In one group of patients, gastro-intestinal symptoms appear within a few hours after the ingestion of infected meat and may continue until manifestations of the invasion of the body by the young parasites appear. In another group of patients there is no immediate effect, but after an interval of 6 to 14 days symptoms associated with the dissemination of the larvæ through the blood stream occur. This difference in the onset has not been explained, but it is possible that it is due to variation in dosage.

When the infection is severe the disease can be divided into three stages:

1. The stage of intestinal infestation—the symptoms are referable to the gastro-intestinal tract and usually begin within a few hours after ingestion of infected meat. Nausea, vomiting, diarrhea and abdominal cramps are usually present and the temperature rises gradually. There is considerable prostration with pain and stiffness in the muscles.

2. The stage of dissemination—the embryos usually enter the blood and lymph stream about the end of the first week. Edema of the face and eyelids is common at this period, but its mechanism is not clearly understood. Fever and profuse sweating are often present. The muscles, especially those of respiration, mastication and the eye, are painful and their function is disturbed. Bronchitis may be present and the patient is inclined to be apathetic and prostrated.

3. The stage of encystment—about the end of the sixth week the



TABLE 1.—CLINICAL DATA ON 23 CASES OF TRICHINOSIS.

Case.	Date.	Age.	Sex.	Presenting complaints.	History.	Maximum W.B.C. in thous.	Maximum eosinoph., %.	Fever.	Muscle tenderness.	Edema.	Biopsy.	Outcome.
1	10/ 5/31	22	M	Malaise, aching, fever, sore throat	Unessential	27.2	57	Intermittent	No	No	Inflammatory infiltration, eosinophils, no parasites	Recovered.
2	11/13/31	17	F	Pain in extremities, edema, abdominal tenderness	Ingestion of raw pork 6 wks. before	16.4	4	Remittent	Yes	Legs, arms, eyelids	Myositis, trichinae at autopsy	Died 7 days after admission.
3	3/28/32	37	F	Edema, headache, vomiting	Unessential	8.1	24	Intermittent	Yes	Legs, eyelids	Myositis, no parasites	Recovered.
4	7/13/32	20	F	Muscle pain, malaise, anorexia, weakness, fever	Ingestion of raw pork and beef	16.1	32	Remittent	Yes	Eyelids	Not permitted	Recovered.
5	7/13/32	28	M	Weakness, daily fever	Ingestion of raw pork and beef	25.8	12	Intermittent	No	No	Inflammatory infiltration between muscle fibers, no parasites	Recovered.
6	8/19/32	18	M	Edema	Ingestion of bologna	14.3	11	None	No	Eyelids and face	No parasites	Recovered.
7	5/ 7/34	23	M	Backache, edema	Unessential	19.3	45	None	Yes	Ankles, arms, face	Myositis, lymphatic infiltration	Recovered.
8	7/28/34	26	F	Edema, headache, fever	Unessential	10.5	51	Intermittent	No	Eyelids and face	Inflammatory reaction, trichinae found	Recovered.
9	6/29/34	23	M	Muscle pain, sore throat, vomiting	Ingestion of pork	17.7	30	Intermittent	Yes	Eyelids	No parasites	Recovered.

	10	8/17/34	23	F	Pain in legs and abdomen	Unessential	17.9	59	Slight	Yes	No	No parasites	Recovered.
11	11/ 4/34	20	F	F	Edema, muscle pain, headache	Ingestion of raw pork	13.0	23	Remittent	Yes	Eyelids	Inflammatory infiltration, eosinophils, no parasites	Recovered.
12	9/17/35	19	M	M	Edema, muscle pain	Ingestion of cooked sausage	24.1	51	Remittent	Yes	Eyelids	Inflammatory infiltration, eosinophils	Recovered.
13	7/18/36	28	M	M	Diarrhea, abdominal pain	Ingestion of poorly cooked pork	14.0	47	No	No	No	Inflammatory reaction, no parasites	Recovered.
14	12/30/36	57	M	M	Vomiting diarrhea, weight loss	Unessential	14.0	52	No	No	No	No parasites	Recovered.
15	1/ 7/37	34	M	M	Diarrhea, malaise, weakness	Ingestion of raw pork	19.3	16	Intermittent	Yes	Yes	Trichinae present	Recovered.
16	8/12/37	22	F	F	Diarrhea, vomiting, headache	Ingestion of raw pork	28.0	73	Intermittent	No	Eyelids	Inflammatory infiltration, eosinophils	Recovered.
17	2/27/37	37	M	M	Diarrhea, malaise, insomnia	Ingestion of raw pork	17.3	37	Slight	No	No	Inflammatory reaction, no parasites	Recovered.
18	10/ 2/37	30	F	F	Muscle pain, edema	Ingestion of raw pork	5.3	11	Remittent	Yes	Eyelids	Trichinae present	Recovered.
19	4/18/38	21	M	M	Chills, malaise, pain in legs	Ingestion of rare pork	12.2	37	Slight	Yes	Face	Not permitted	Recovered.
20	5/ 3/38	50	F	F	Chills, vomiting, pain in legs and abdomen	Ingestion of poorly cooked pork	9.3	38	Slight	Yes	No	Focal myositis, inflammatory infiltration, eosinophils, no parasites	Recovered
21	6/15/32	43	F	F	Vomiting, delirium, meningeal symptoms	Ingestion of pork	21.8	12	Yes	Yes	Yes	Diagnosis of trichinosis at autopsy	Died.
22	7/10/33	40	M	M	Vomiting, diarrhea	Ingestion of bologna	18.0	38	Yes	Yes	Yes	Trichinae present	Recovered.
23	10/25/30	32	M	M	Edema	Ingestion of hamburgers	14.5	21	Slight	Yes	Yes	Trichinae present	Recovered.

embryos become encysted in the muscles. At this time the symptoms become less severe and the temperature gradually returns to normal. The patient is anemic and emaciated and the edema subsides gradually. This late edema is probably due to renal involvement and cachexia. The muscular pains and weakness may persist for several months.

Early in the disease there is a marked increase in the percentage of red blood cells and a moderate increase in the percentage of hemoglobin. Later anemia develops, the number of red cells falling as low as 2,500,000 per c.mm. and the hemoglobin as low as 45%. Leukocytosis, usually about 25,000 white blood cells per c.mm., is often found. When the embryos invade the tissues, the eosinophils increase to 15 to 30% or more; in 1 of our cases an eosinophilia of 73% was found.

Beside these manifestations which constitute the clinical picture of the typical case of trichinosis, other less common signs and symptoms have been reported. General fatigue, generalized edema, cough, headache, chills, furuncles and hoarseness were found in the cases of McDonald and Waddell.<sup>23</sup> In the more severe cases, Cheney<sup>9</sup> and Carlson<sup>7</sup> noted a marked hypotension. The heart in patients with trichinosis has been studied and both clinical and electrocardiographic evidences of various degrees of temporary myocardial involvement were reported by Spink,<sup>32a</sup> Cushing<sup>11</sup> and Beccher and Amidon.<sup>5</sup> The spleen may be palpable and this condition may persist for several months according to Reifenstein, Allen and Allen.<sup>29</sup>

Conner<sup>10</sup> describes some of the deviations from the usual clinical picture of the disease that may be seen. Some cases may run an afebrile course. The characteristic eosinophilia may be lacking throughout the whole course or for the first few weeks of the disease. Occasionally a positive Widal reaction makes the differentiation from typhoid fever difficult. A few cases resemble acute nephritis or meningitis, and at times there may be alarming throat symptoms or a frontal sinusitis. In a small percentage of cases epigastric pain is the chief or only symptom.

Frequently trichinosis is complicated by the involvement of various organs. Ocular manifestations, such as chemosis, exophthalmos, conjunctival ecchymosis, mydriasis and retinal hemorrhage were described by Carter.<sup>8</sup> Neurologic and mental symptoms were present in some of the patients reported by Merritt and Rosenbaum<sup>24</sup> and Most and Abeles.<sup>26</sup> Herrick<sup>19</sup> and Kilduffe, Barbash and Merendino<sup>21</sup> noted instances of femoral phlebitis and femoral thrombosis, and pneumonia occurred in several cases cited by McDonald and Waddell.<sup>23</sup>

*Special Diagnostic Aids.* In 1928, Bachman demonstrated precipitins in the serum of individuals infected with the *Trichinella spiralis*<sup>4a</sup> and also noted that a specific local skin reaction followed the injection of trichinella protein.<sup>4b,c</sup> He concluded that as an aid

in diagnosis the skin reaction is easy and more practical than the precipitin test, since typical skin reactions appear 20 to 30 days before precipitins are demonstrable in the blood stream. Some investigators (McCoy, Miller and Friedlander,<sup>22</sup> Kilduffe,<sup>20</sup> Spink and Augustine,<sup>33</sup> Heathman<sup>18</sup>) have found that these special diagnostic aids are not entirely reliable and that the presence of eosinophilia and muscle biopsy are more practical and valuable. However, in ruling out trichinosis and detecting mild, sporadic and atypical cases the Bachman skin test may be a valuable aid (Friedlander,<sup>13</sup> Spink and Augustine,<sup>33</sup> Spink,<sup>32b</sup> Augustine<sup>3</sup>). Hall<sup>15</sup> reported 8 cases of trichinosis all of which gave a positive reaction to the intradermal, and Blumer,<sup>6a</sup> Vener and Stevens<sup>35</sup> and Schapiro, Crosby and Sickler<sup>31</sup> have all found that positive reaction occurs early in the disease. Our experience has been that the blood counts, muscle biopsy and skin test are all of value as diagnostic aids.

**Summary.** The following points summarize the safeguards that we believe should be used for the control of trichinosis:

1. Individuals by their food habits expose themselves to the disease and the public should, therefore, be informed of the danger of trichinosis. They should be taught emphatically that insufficiently cooked food containing any pork is dangerous. The consumer must be brought to realize that he is, in the last analysis, responsible for getting trichinosis.

2. As Pote<sup>27</sup> points out, the least likely source of the parasite is pork products prepared under Federal and adequate municipal supervision. We agree with his theory that it is the unprocessed pork products, especially summer sausage, prepared without supervision in small local slaughter houses or on farms, that frequently cause trichinosis. The jurisdiction of public health organizations should be made to include these sources of pork products.

3. The packer and swine grower, as pointed out by Hall,<sup>16c</sup> have it within their power and should be given the responsibility of setting up safeguards against the consumption of infested pork, particularly by excluding the hog which is fed uncooked pork scraps.

4. The medical profession should keep in mind the possibility of the disease when unusual cases of "flu" or "grippe" do not respond readily to treatment. If the physician suspects the disease the diagnosis usually will be made readily. All cases should be reported to the Health Department and attempts made to discover the source of the parasite.

Finally, we should like to emphasize that while the immediate responsibility for contracting trichinosis rests upon the consumer, the United States Public Health service should assume the chief rôle in protecting the public from this disease.

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## STUDIES WITH THE AGAR CUP-PLATE METHOD.

### II. THE EFFECT OF BLOOD ON MERCURY ANTISEPTICS.

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ALTHOUGH mercury compounds yield remarkably high phenol coefficients (Thomas;<sup>13</sup> Birkhaug<sup>3b</sup>), it is well known that they are influenced markedly by protein (Abbott;<sup>1</sup> Smith, Czarnetzky and Mudd;<sup>12</sup> and others). Therefore a high phenol coefficient for a given mercurial does not presuppose comparable effectiveness in the presence of blood. On the contrary, as will be shown, such data may be meaningless and even misleading.

The high antiseptic values of organic mercurials has stimulated the study of these substances in the intravenous treatment of experimental and clinical bacteremias. However, such investigations have yielded conflicting data. For example, Raiziss, Severac, and Moetsch<sup>9</sup> reported favorable results when metaphen was used for the treatment of artificial *Staph. aureus* bacteremia in rabbits.

Similarly, Lambert<sup>6</sup> obtained encouraging results with the use of merthiolate in clinical tuberculosis, and Barthelme<sup>2</sup> found a lowered mortality rate in tularemia when patients were treated intravenously with metaphen. On the other hand, Douglas and Birk-

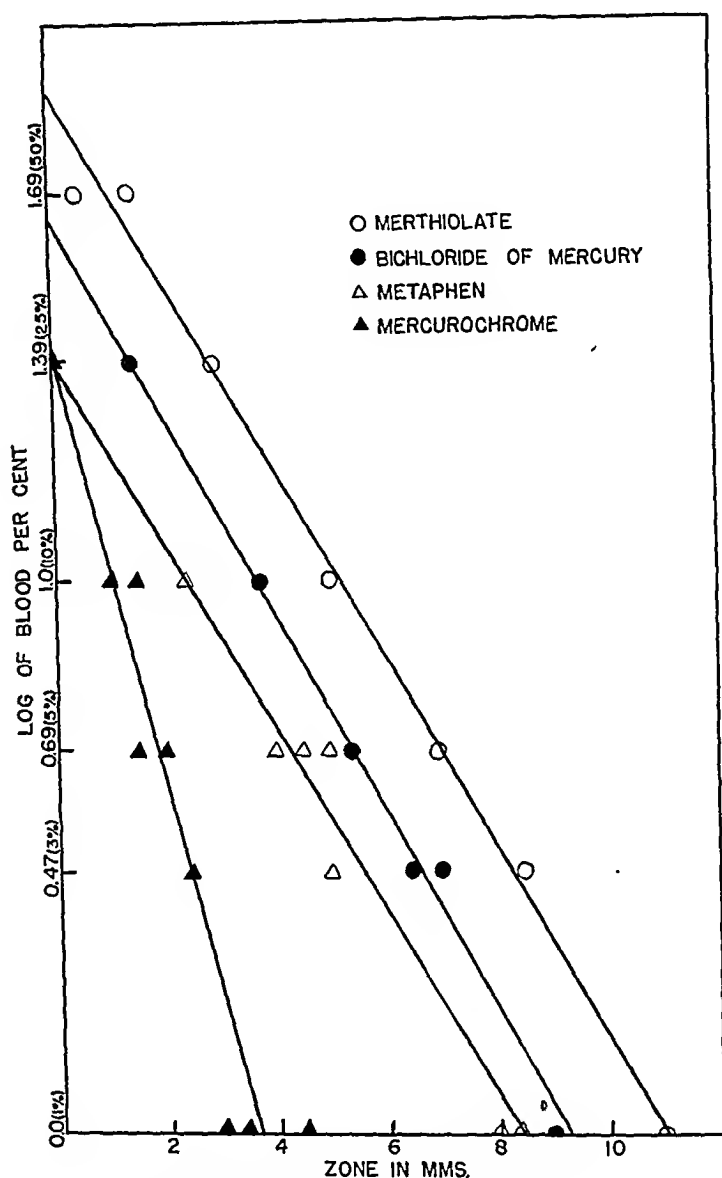


CHART 1.—Zone in millimeters produced by 1 to 1000 dilution of mercurial antiseptics in varying concentrations of blood. As the blood concentration increases, the size of the zone of inhibition for *Staph. aureus* decreases. The relative potency of the four mercurials is evident.

haug<sup>5</sup> found that metaphen accelerated a fatal issue in experimental bacteremia with pneumococcus Type I, and Cummins,<sup>4</sup> Mallick, Ali and Singh<sup>7</sup> failed to obtain favorable results in the treatment of clinical tuberculosis with intravenous merthiolate medication.

The discrepancy between the known potency of mercurials as determined by the phenol coefficient method and their disputed potency *in vivo* appears to be associated with the blood factor (Simmons;<sup>11</sup> Birkhaug<sup>8a</sup>). Therefore, it is clear that the limits of activity of mercury compounds in the presence of whole blood should be determined before the use of these substances receives further serious consideration in intravenous chemotherapy. Our experiment was planned to study such limiting values.

**Technique.** A standardized agar cup-plate method (Rose and Miller<sup>10</sup>) was employed. The test organism was a stock culture of *Staph. aureus* (WP3 strain), grown in broth for 18 to 20 hours, standardized to 1 billion organisms per cc., and used in the ratio of 0.1 cc. to each 30 cc. volume of agar. The basal medium was 3% beef extract agar, pH 6.8; this was mixed with equal volumes of either defibrinated horse blood\* or horse blood-saline dilutions to make an agar concentration of 1.5%. Blood agar plates with the following blood content were prepared: 1%, 3%, 5%, 10%, 25%, and 50%. When the medium hardened, cups were made by removing discs of agar 1.5 cm. in diameter. Aqueous 1 to 1000 dilutions of mercurochrome, metaphen, merthiolate,† and mercury bichloride were prepared. A 1 to 500 aqueous solution of metaphen was used as a stock solution because the powder was not available. All dilutions of the other mercurials were made by dissolving accurately weighed powder in double distilled water. Each antiseptic in 0.2 cc. amounts was placed in cups of the various blood agar media. After 24 hours' incubation at 37° C., the zone of inhibition of bacterial growth was measured and recorded in millimeters. The log of the blood concentration (ordinate) was plotted against the zone size (abscissa). The results of the experiment are shown in Chart 1.

The four antiseptics used showed a decreasing effectiveness in the following order: merthiolate, mercury bichloride, metaphen, mercurochrome. The variation in antibacterial properties is evident from the figure. As the blood concentration rose all compounds showed a diminishing activity. At the 25% blood level, metaphen and mercurochrome were approaching a zero value. Similarly, the activity of mercury bichloride was extinguished somewhat below the 50% blood level, while the antiseptic properties of merthiolate were still in evidence when half the medium consisted of blood. The zone of inhibition of bacterial growth at any blood level may be determined‡ for a given dilution of each mercury antiseptic by applying the general formula ("Law of Organic Growth"),  $C = Ke^{-mz}$ .

C, concentration of blood in per cent; K, a constant for each antiseptic having the value of C when the zone is zero; e, base Napierian log; m, coefficient of inactivation of the antiseptic; z, zone in millimeters.

\* Obtained through the courtesy of the Mulford Laboratories, Sharp and Dohme, Glenside, Pa.

† Obtained through the kindness of the Eli Lilly Co., Indianapolis, Indiana.

‡ We are indebted to Mr. Charles Robb for his invaluable help in the mathematical analysis of the data.

The application of the formula may be illustrated as follows: Let us assume that the zone size in 2% blood is desired for a 1 to 1000 dilution of mercurochrome. For mercurochrome,  $K = 24.55$ ;  $m = 0.875$ .

$$\begin{aligned} C &= Ke^{-mz} \\ &= 24.55e^{-0.875z} \\ \log C &= \log 24.55 - (0.875)z \log e \\ &= \log 24.55 - (0.875)(0.4343)z \\ \text{or } z &= \frac{\log 24.55 - \log C}{0.38} \end{aligned}$$

To determine  $z$  when the blood concentration is 2%:

$$\begin{aligned} z_2 &= \frac{\log 24.55 - \log 2}{0.38} \\ &= \frac{1.390 - 0.301}{0.38} \\ &= 2.8 \text{ mm.} \end{aligned}$$

**Comment.** Our experiments show that organic and inorganic mercury compounds follow a similar pattern of inactivation by blood. The fact that a single mathematical formula applied equally well in all cases lends support to the validity of the data.

No attempt was made to establish the usefulness of mercurials on intact skin surfaces. However, if the skin is broken and blood is present in a wound, the antiseptic value of these substances may be questioned on the basis of our data.

The usual procedure for testing antiseptic potency has been the phenol coefficient technique. However, the data obtained by this method have been inferentially misleading and have encouraged intravenous mercurial chemotherapy. It is clear that mercury compounds should be appraised under circumstances which simulate their application in clinical conditions. The implications concerning the intravenous use of mercurials is obvious.

Studies dealing with the influence of agar *per se* on zone size (Miller and Rose<sup>8a</sup>) and the correlation of agar cup-plate data with an antiseptic-dilution testing procedure (Miller and Rose<sup>8b</sup>) will be presented in separate communications.

**Summary and Conclusions.** Using a standardized agar cup-plate technique, 4 mercury antiseptics (mercury bichloride, mercurochrome, metaphen, and merthiolate) were studied in horse blood-agar mixtures. The blood content of the test media varied from 1 to 50%. The test organism was *Staph. aureus* (WP3 strain).

All 4 mercury compounds showed a diminishing antiseptic effectiveness as the blood concentration was increased. The inactivation of the mercurials was expressed by the general formula,  $C = Ke^{-mz}$ . The limits of activity of the mercurials indicated that these substances had no antiseptic properties at certain critical blood levels. The *in vitro* experimental data suggested that mercury compounds could have no value in intravenous therapy.



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## A NEW DIAGNOSTIC TEST (GALACTOSE) FOR THYROID DISEASE.\*†

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Two years ago we reported finding a consistent reduction of "tolerance" to galactose in a group of 26 patients with hyperthyroidism.<sup>2</sup> This lead was followed by an experimental investigation to discover the cause of this phenomenon, and a clinical study of a larger series of patients to determine whether the galactose tolerance test would be useful in the diagnosis of disorders of the thyroid gland.

This investigation<sup>1</sup> showed that in rats experimental hyperthyroidism caused increased intestinal absorption of sugars, which probably is responsible for the abnormally high values obtained for galactose and for glucose in the blood of patients with hyperthyroidism following tolerance tests with these sugars. Thyroidectomy in rats was found to result in decreased absorption of glucose, which offered a more rational explanation than increased utilization of sugar for the low glucose tolerance curves characteristic of patients with myxedema. Evidence was obtained to indicate that increased absorption of sugars was probably due to stimulation of phosphorylation in the intestinal mucosa by thyroxin.

\* Read before the Annual Meeting of the Association for the Study of Goiter at Cincinnati, May 22-24, 1939.

† Aided by a grant from the Christine Breon Fund for Medical Research.

In the present paper we are reporting our clinical experiences with the galactose tolerance test in 130 patients with hyperthyroidism, 121 individuals without hyperactivity of the thyroid gland and 7 patients with myxedema.

**Technique of the Test.** Forty grams of galactose (Pfanstiehl) dissolved in 400 cc. of water and flavored with lemon juice were administered by mouth after the patient had fasted over night. Specimens of blood were obtained from the cubital vein before, and 5, 15, 30, 60 and 120 minutes\* after administration of galactose.

The glucose fraction of the blood was removed by fermentation with ordinary yeast according to the method of Somogyi<sup>2</sup> as modified by Raymond and Blanco.<sup>3</sup>

**Preparation of Yeast.** A weighed amount of fresh commercial yeast (Fleishman's) is suspended in 5 to 10 parts of water, centrifuged, and decanted. This is repeated until the supernatant liquid is clear and colorless and gives no reduction test (6 to 7 washings). The yeast is then suspended in 10 parts of water. In this condition, it will keep well in a refrigerator for about 2 weeks.

**Use of the Hagedorn-Jensen Method.** Two-tenths cubic centimeters of blood is collected into an accurately calibrated pipette (we use 0.2 ml. in 0.001 ml. Kahn pipette No. 37036); and transferred to 2.3 cc. of distilled water, rinsing the pipette once or twice with the solution. One cubic centimeter of the 10% yeast suspension is then added, the contents mixed by tapping the tube against the hand, and after 4 or 5 minutes 0.5 cc. of tungstic acid solution (prepared freshly by mixing equal volumes of 10%  $\text{Na}_2\text{WO}_4$  and  $\frac{2}{3}$  N  $\text{H}_2\text{SO}_4$ ) is added. The test tube is covered with the thumb and the contents are mixed quickly by inverting. After standing a few minutes, the mixture is centrifuged at high speed. One cubic centimeter of the clear filtrate is used for titration.

**Use of the Folin-Wu Method.** The yeast is washed in the usual manner and a 20% yeast suspension is prepared. To 2 cc. of oxalated blood, 14 cc. of the yeast suspension and 4 cc. of the tungstic acid solution are added. This mixture is filtered, and 2 cc. portions of the filtrate are used for sugar determinations.

The figure for non-fermentable reducing substances in the fasting blood is subtracted from the corresponding figure in the remaining specimens to obtain the galactose content of the blood titrated as glucose. In order to obtain the true value for galactose, which has a lower reducing power than glucose, 24% must be added to the last figure.

Galactose is used in this test because, while having a rate of absorption very similar to that of glucose, it has the advantage that, unlike glucose, it can be identified in the blood.

**Results.** NORMAL SUBJECTS AND PATIENTS WITHOUT HYPERTHYROIDISM. In 10 normal volunteers, blood galactose curves for 2-hour periods were obtained. The composite curve of the results is shown in Figure 1. It reaches a maximum of 19 mg.% at the end of 60 minutes. The peaks of the individual curves ranged between 13 and 31 mg. per 100 cc. and were found to occur in approximately one-half the patients in the 30-minute specimen, and in the other one-half in the 60-minute specimen. In the 5-minute specimen,

\* At present we consider the 15- and 120-minute specimens unnecessary, and the 5-minute specimen relatively unimportant except when the test is repeated on account of borderline results.

galactose in very small amounts (up to 4 mg. per 100 cc.) was present in only 2 instances. At the end of 2 hours, galactose in small amounts was present in the blood only exceptionally.

The galactose tolerance test was used also in 87 patients suffering from diseases other than hyperthyroidism or myxedema (Fig. 1).

Almost all of the patients with the following diseases were found to have normal or low galactose tolerance curves: diabetes mellitus, Addison's disease, acromegaly (in the late stages), Cushing's disease, osteitis fibrosa cystica, spontaneous hypoglycemia, congestive heart

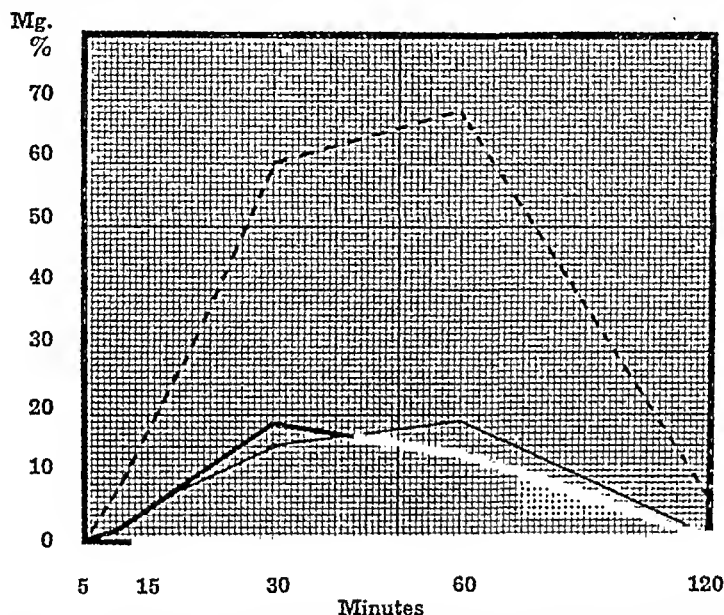


FIG. 1.—Average galactose tolerance curves of 10 normal individuals (narrow line), 87 patients without hyperthyroidism or myxedema (wide line), and 130 patients with clinical hyperthyroidism (broken line).

failure, vascular hypertension, secondary anemia, peptic ulcer, carcinoma of the stomach, idiopathic ulcerative colitis, rheumatoid arthritis, osteosarcoma, syphilis, pellagra, anorexia nervosa, diarrhea, intestinal hypermotility and menopause.

In a single case of each of the following conditions there was an abnormally high galactose curve in the blood: diabetes mellitus,\* congenital syphilis with chronic mastitis, hyperinsulinism, intractable gastric ulcer of long standing, intestinal hypermotility, Cushing's disease and prolonged fever of unknown origin.

The distribution of the peaks of the galactose curve in normal subjects and in patients without hyperthyroidism is shown in Figure 2.

**HYPERTHYROIDISM.** The galactose tolerance test was given to 130 patients with clinical symptoms and signs of hyperthyroidism;

\* One case out of 15.

in all cases the diagnosis was made by the Thyroid Committee of the University of California Hospital.\* In difficult cases, the final diagnosis was made only after periods of observation and treatment that lasted for weeks or months.

The composite curve of the galactose tolerance test in our cases of hyperthyroidism is given in Figure 1. It reaches a maximum of 68 mg. per 100 cc. in the 60-minute specimens. The peaks of individual curves varied from 25 to 152 mg. per 100 cc. (Fig. 2). As in the case

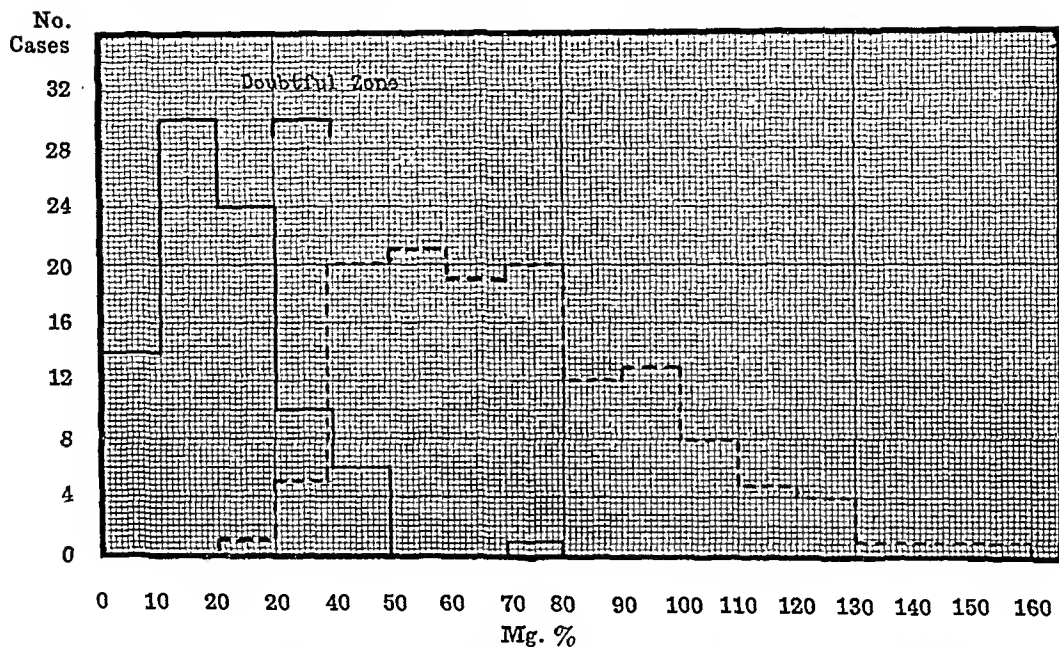


FIG. 2.—Distribution of the maximal galactose values in the blood of 87 patients without hyperthyroidism or myxedema (solid line), and of 130 patients with hyperthyroidism (broken line).

of normal subjects, about one-half of the peaks occurred in the 30- and one-half in the 60-minute specimens. Most patients with hyperthyroidism had some galactose in the 5-minute specimen of blood, and in one-half of the cases the amount was between 9 and 20 mg. per 100 cc. At the end of 2 hours, galactose was seldom found in the blood. The distribution of the readings of the basal metabolic rates in patients of this group is given in Figure 3. When several basal metabolic rate estimations were obtained on the same patient, the test most nearly concurrent with the galactose tolerance test was chosen.

**EFFECTS OF THYROIDECTOMY.** In 22 cases, the galactose tolerance test was repeated after thyroidectomy. (See Fig. 4.) In these 22 cases, 18 of the curves returned to normal range after operation, 2 were lower than the corresponding preoperative curve

\* This committee, which holds weekly conferences, consists of a group of internists and surgeons and one radiologist, who are making a special study of diseases of the thyroid gland.

but remained within the pathologic range, and 2 were unchanged at the time of discharge from the hospital. Of these last 2 patients, 1 had had a preoperative basal metabolic rate of 21%+, which was reduced by the operation only to 14%+.

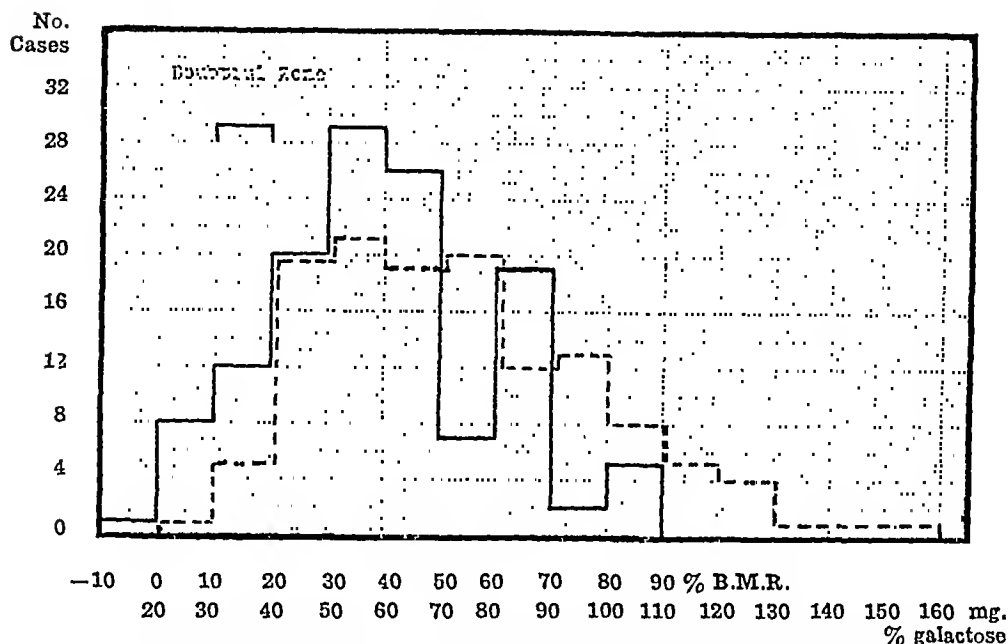


FIG. 3.—Distribution of the B.M.R. (solid line) and the maximal galactose values in the blood of 130 patients with clinical hyperthyroidism (broken line);

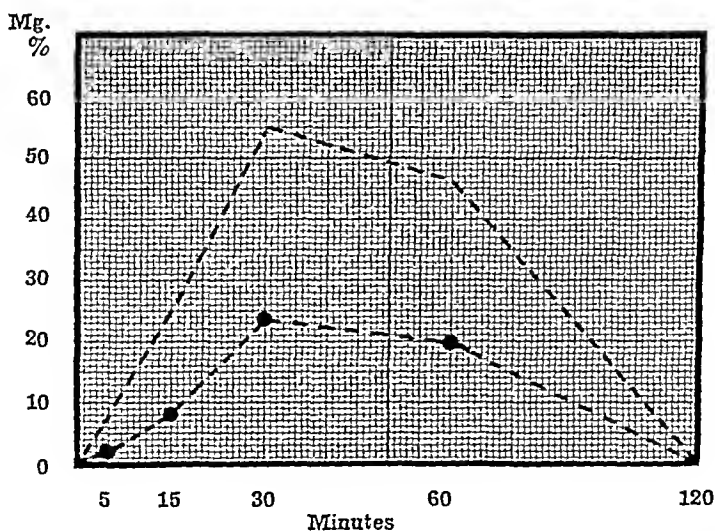


FIG. 4.—Average galactose tolerance curves of 22 patients who had thyroidectomy for hyperthyroidism before (broken line) and after operation (broken line with discs).

*Myxedema.* Six patients with spontaneous myxedema and basal metabolic rates ranging between 19 and 33%— had galactose tolerance curves with peaks from 3 to 11 mg. per 100 cc. One patient with postoperative myxedema and a basal metabolic rate of 27%— was found to have no galactose in the blood during the galactose tolerance test.

CONDITIONS CLINICALLY SIMULATING HYPERTHYROIDISM WITH NORMAL GALACTOSE TOLERANCE. In this classification, we were interested in three conditions:

1. *Anxiety With Hyperventilation.* The basal metabolic rates of 8 patients in this group were elevated to between 22 and 36%+. The maximum galactose content of their blood was between 18 and 35 mg. per 100 cc.. Of 13 other patients with anxiety states that clinically suggested hyperthyroidism but had basal metabolic rates under 16%+, 11 had peaks of the galactose curve between 9 and 30 mg. per 100 cc., 2 had peaks of 46 and 49 mg. per 100 cc. respectively.

2. *Diseases of the Heart With Increased Basal Metabolic Rate Estimations.* Four patients with cardiac lesions who had basal metabolic rates between 24 and 32%+ were referred to us with the diagnosis of hyperthyroidism. The peaks of the galactose curves in these patients were between 9 and 36 mg. per 100 cc.

3. *Diseases of the Thyroid Gland Other Than Hyperthyroidism.* Three patients with non-toxic adenoma of the thyroid had a maximal galactose content of the blood between 11 and 24 mg. per 100 cc. Two patients with Hashimoto's struma and basal metabolic rates of 9%+ and 44%+ had the peak of the galactose curve at 4 and 33 mg. per 100 cc. respectively.

DISEASES OTHER THAN HYPERTHYROIDISM WITH ABNORMAL GALACTOSE TOLERANCE. 1. *Diseases of the Liver.* In 11 patients with deep jaundice due to parenchymatous diseases of the liver, we found a true impairment of tolerance to galactose as shown by the rate of disappearance of galactose injected intravenously. Therefore high blood galactose curves after oral tolerance tests with this sugar may be expected in cases of marked functional insufficiency of the liver. This actually occurred in several patients in whom the oral galactose tolerance test was done to test this assumption. A separate report will deal with our work on galactose tolerance in patients with hepatic diseases.

2. *Paget's Disease.* Fifteen of 18 patients with this condition were found to have higher than normal galactose tolerance curves, apparently due to increased intestinal absorption. Our data on patients with Paget's disease will be published in another paper.

The results of galactose tolerance tests on patients with hepatic involvement and with Paget's disease are not included in Figures 1 and 2.

REPETITION OF THE GALACTOSE TOLERANCE TEST. In 10 patients with or without hyperthyroidism, the galactose tolerance test was

repeated in order to determine the degree of uniformity of the resulting curves. In 1 case the difference between the peaks of successive tests was 40 mg.,\* in another 21 mg., in 2 cases 9 mg. and in 6, 3 mg. or less.

**INTRAVENOUS ADMINISTRATION OF GALACTOSE.** It was important to determine whether inability to utilize galactose due to hepatic insufficiency played a part in producing the abnormally high galactose tolerance curves in our patients with hyperthyroidism. For this purpose, 10 patients with hyperthyroidism, who had very high maximal blood galactose values averaging 87 mg. per 100 cc. after the oral test, were given 40 gm. of galactose intravenously. Then the rate of disappearance of galactose from the blood was determined and compared with that of 10 normal subjects and of 11 patients with parenchymatous diseases of the liver. This comparison showed that in patients with hyperthyroidism tested by the intravenous method, the utilization of galactose was within normal limits.

One patient with myxedema and a maximal blood galactose value of 3 mg. per 100 cc. had an abnormally prolonged galactose curve in the blood following intravenous administration of this sugar.

**Comment.** From the distribution of the peaks of the galactose curves in subjects with and without hyperthyroidism (Fig. 2), it is seen that in round figures, the normal range for the maximal concentration of galactose in the blood under the conditions of our test is between 10 and 30 mg. per 100 cc. A peak between 30 and 40 mg. per 100 cc. in the galactose tolerance curve lies in the doubtful range. Values exceeding 40 mg. per 100 cc. for galactose in the blood are abnormal. So also are maximal values below 10 mg. per 100 cc. Repetition of the test in the same person usually gives fairly uniform maximal values. When these criteria were applied to our group of 130 patients with hyperthyroidism, the galactose tolerance test was positive in 124 cases, doubtful in 5 and negative in 1. In a group of 87 patients with conditions other than hyperthyroidism, proven hepatic insufficiency, or Paget's disease, the outcome of the test was positive in 7 instances, doubtful in 10 and negative in 70. In 4 of the 7 patients with a positive outcome of the test, involvement of the liver was suspected. The galactose tolerance curve was abnormally low in 6 out of 7 patients with myxedema, and barely within the lower limit of normal in 1.

In the normal state, little if any galactose is found in the 5-minute specimen. In hyperthyroidism, increased intestinal absorption of sugars is expressed not only by a high peak of the galactose curve but also, in about one-half of the cases, by a premature appearance in the blood of considerable amounts of galactose. Therefore the finding of 10 mg. per 100 cc. or more of galactose in the 5-minute

\* This was in a patient with hyperthyroidism who in 2 tests had peaks of 90 and 50 mg. per 100 cc. but was treated with Lugol's solution between the tests.

specimen is an additional criterion in favor of the diagnosis of hyperthyroidism. This criterion is naturally most useful in instances where the peak of the galactose curve is in the doubtful zone.

A comparison in hyperthyroid patients of the results of the galactose tolerance test with their basal metabolic rates\* shows that no close quantitative correlation between the two exists, although usually patients with very high basal metabolic rates also have very high values for galactose in the blood. The reason for such a lack of correlation is not clear. Administration of a standard amount of galactose regardless of body weight probably does not explain it, because 40 gm. galactose exceed the capacity for intestinal absorption during the period of the test. Moreover, the correlation was no greater when the two tests were compared in groups of patients classified according to weight. Probably the best explanation is that elevation of the basal metabolic rate and stimulation of absorption are relatively independent effects of thyroxin which occur to varying degree in different patients. This possibility is also suggested by our experimental data<sup>1</sup> showing that an increase in basal metabolism produced by administration of alpha-dinitrophenol or by overheating had no stimulating effect on the intestinal absorption of glucose.

The well-known occurrence of true hyperthyroidism without elevation of the basal metabolic rate is also in favor of this conception. An interesting example of this condition was encountered during the present study. Mr. H., aged 42, entered with a clinical picture typical of Graves' disease, but by repeated estimations his basal metabolic rate was found to be between 5 and 10%-. A galactose tolerance test showed 10 mg. per 100 cc. of this sugar in the 5-minute specimen and 55 mg. per 100 cc. at the peak of the curve. After much debate in the Thyroid Committee, the patient was subjected to a subtotal thyroidectomy. Microscopic examination of the thyroid gland showed characteristic hyperplasia. Following operation the patient lost his symptoms and signs indicative of hyperthyroidism. A repetition of the galactose tolerance test showed no galactose in the 5-minute specimen and a maximum of 21 mg. per 100 cc. of galactose in the blood. Several basal metabolic rate determinations averaged only about 5% lower than before operation.

In comparing the clinical value of the galactose tolerance test with that of the basal metabolic rate, it appears that among patients with definite clinical hyperthyroidism doubtful results† are encountered somewhat less frequently with the galactose tolerance test (Fig. 3). This is probably due to the fact that the intestinal absorption of sugars is more sensitive to the influence of a small

\* In this study, the basal metabolic rates were estimated for 8-minute periods by the indirect method with the Benedict-Roth apparatus and the use of the nose clip.

† Defined for the galactose tolerance test as under 40 mg. per 100 cc. and for the basal metabolic rate as under 10% plus.



excess of circulating thyroxin than is the basal metabolism. At least Russell<sup>4</sup> in a study undertaken at our suggestion found that in rats after hypophysectomy, which depresses both the absorption of sugars and the basal metabolic rate due to lack of the thyrotropic hormone of the anterior lobe of the hypophysis, administration of thyroxin in amounts sufficient to restore normal intestinal absorption raised the basal metabolic rate only half-way back to the original normal level.

When the basal metabolic rate is found to be definitely elevated in patients with hyperthyroidism, that test seems to offer a more accurate index of the degree of hyperthyroidism than does the galactose tolerance test.

In the differential diagnosis of hyperthyroidism, the galactose tolerance test is useful in cases of low grade hyperthyroidism, especially when the B.M.R. is less than 20%+ and in patients without hyperthyroidism who have an abnormally elevated B.M.R. Fifteen of our 130 patients with hyperthyroidism belong in the first classification, and in all of these the galactose test was positive. It is of interest that the proportion of patients with low grade hyperthyroidism in our series was almost identical with that recently reported by Young and Krantz.<sup>6</sup> In the second classification were 8 patients suffering from anxiety states with hyperventilation, and 4 patients with obscure cardiac dyspnea. The B.M.R. in these 12 patients ranged from 22 to 36%+, whereas the galactose test was negative in 10 cases and doubtful in 2\*.

In 5 patients with non-toxic adenoma of the thyroid or with Hashimoto's struma, the results of the galactose tolerance test corresponded to estimations of the B.M.R.

Advanced hepatic insufficiency and Paget's disease interfere with the use of the galactose tolerance test for the diagnosis of hyperthyroidism. However, since in hepatic insufficiency there is a true impairment of utilization of galactose whereas in hyperthyroidism the high galactose tolerance curve is due to increased intestinal absorption, this difference can be brought out by administering the galactose again at a later date intravenously and following the rate of its disappearance from the blood. In this connection it must be remembered that several authors, including ourselves, have found hepatic insufficiency as indicated by various liver function tests to be present in some patients with severe hyperthyroidism.<sup>2</sup>

Intravenous administration of galactose to patients with hyperthyroidism showed that, as a rule, utilization of galactose in this condition is normal. This finding represents a clinical confirmation of our experimental work on animals indicating increased intestinal absorption in hyperthyroidism.

As a rule, subtotal thyroidectomy promptly restores the blood

\* A patient with myeloid leukemia and a B.M.R. of  $\frac{1}{2}$ %+ also had a normal galactose test.

galactose curve to normal, but occasionally it fails to accomplish this. Unfortunately, we were unable to repeat the galactose tolerance test on our 2 patients in whom the galactose curve had remained unchanged after operation. A possible explanation of these unchanged curves is that the amount of thyroid tissue removed in these cases at operation may have been insufficient. This is suggested by the great sensitivity of intestinal absorption to thyroxin and by the fact that in 1 of the 2 cases thyroidectomy also produced little change in the basal metabolic rate.

Our experience with 7 patients who had myxedema suggests that the galactose tolerance test could be used also in the diagnosis of doubtful cases of this disease. Intravenous administration of galactose to 1 patient with myxedema indicated a reduced capacity to metabolize galactose. This tends to confirm our conclusion based on experimental data that diminished intestinal absorption of sugars rather than their increased utilization accounts for the low sugar tolerance curves in myxedema.

In communities where no machine for the estimation of the basal metabolic rate is available, the galactose tolerance test can be used instead as a routine procedure for the diagnosis of hyperthyroidism, provided there are facilities for making blood sugar determinations.

**Summary.** 1. A new clinical test for activity of the thyroid gland based on the rate of intestinal absorption of galactose is described. It consists of oral administration of galactose followed by determinations of galactose in the blood 30 and 60 minutes later.

2. Data from 121 control subjects and 130 patients with hyperthyroidism show that the average maximal concentration of galactose in the blood of patients with hyperthyroidism was three times greater than normal and that clinically the test was comparable in reliability to estimations of the basal metabolic rate.

3. Following thyroidectomy, the galactose tolerance test was normal in almost all cases.

4. Advantages of the galactose test are that it is more sensitive than the basal metabolic rate in cases of low grade hyperthyroidism, and that its outcome is not influenced by hyperventilation in anxiety states or by cardiac dyspnea. A disadvantage of the test is that the presence of hepatic insufficiency or of Paget's disease interferes with its use for the diagnosis of thyroid disease.

5. In myxedema abnormally low galactose tolerance curves were observed, indicating that the galactose test can be used also in the diagnosis of this condition.

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## PHARMACOLOGIC AND PATHOLOGIC EFFECTS OF REPEATED CONVULSANT DOSES OF METRAZOL.

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SEVERAL studies have been published recently concerning the toxic effects and pathologic tissue changes resulting from insulin shock therapy (Ferraro and Jervis<sup>6</sup>). Little is known as to the corresponding effects of metrazol (cardiazol, pentamethylenctetrazol). In view of the recent extensive use of metrazol, as well as insulin with metrazol, in the treatment of schizophrenia, the following investigations were undertaken.\*

**Recent Literature.** De Morsier, Georgi and Rutishauser<sup>16</sup> examined 2 rabbits. The first animal, having received a total of 4.5 cc. of cardiazol in 9 injections within 1 month, had severe epileptic convulsions and was killed by bleeding. The second animal, after receiving 2 cc. of cardiazol in 1 injection, died 25 minutes later in a status epilepticus. Postmortem examinations revealed no unusual findings in the first rabbit, but a generalized hyperemia, most pronounced in the brain, in the second rabbit. The tissues appeared normal histologically.

Stender<sup>21</sup> examined 3 rabbits and 2 cats which had been treated with convulsant doses of cardiazol. There were 2, 25 and 31 seizures in the rabbits and 28 and 32 seizures in the cats. The findings for the most part were not significant. There were subpial hemorrhages in 2 rabbits and very small foci of softening in the brain in 1 rabbit. The author expressed the belief that these changes were of traumatic origin, caused by injuries incurred during the convulsions. In the younger cat there were some changes, similar to ischemic changes, in the nerve cells in the cortex and in the hippocampus. However, these findings were considered to be of no significant value.

\* We are much indebted to Dr. Franklin G. Ebaugh, Director of the Colorado Psychopathic Hospital, for suggesting that a systematic histologic study be made of tissues from animals experimentally treated with metrazol.

Reitmann<sup>19</sup> studied 2 dogs: the first, weighing 8 kg., received a total amount of 38.3 cc. of cardiazol within 9 days and the second, weighing 12 kg., an amount of 68.5 cc. within 12 days. Histologically, the second dog exhibited much more severe changes. The vessels generally were dilated and in some places there was stasis. There were many hemorrhages in various places in the cortex as well as subarachnoid and intraventricular hemorrhages. No pathologic changes were revealed in the walls of vessels in the center of the hemorrhages. Several ischemic foci were present in the cortex and in the hippocampus. In places diffuse degeneration of nerve cells was associated with pericellular incrustations and dislocation of nerve cells. As a result of such studies, Reitmann emphasized that cardiazol may cause pathologic changes in the brain which obviously are due to circulatory disturbances. These changes resemble the findings of Stief and Tokay<sup>22</sup> in experimental insulin intoxication. Reitmann stressed the fact that he employed larger toxic doses in the experimental animals than are usually given to human beings in the metrazol treatment of schizophrenia. He was reluctant, therefore, to draw conclusions as to possible results occurring in the human brain following the use of metrazol in treatment.

Hayman and Brody<sup>9</sup> recently reported a fatal case, with autopsy, following metrazol therapy in schizophrenia. The cause of death in this case was considered to be the toxic effect of metrazol upon a pathologically impaired heart. The pathologic changes consisted of a preëxistent chronic endocarditis together with marked congestion of all the organs. No characteristic lesion in the brain or the other organs was found at autopsy. The authors mentioned 3 other fatal cases following metrazol therapy in schizophrenia, none of which showed any significant lesions in the brain and in all of which there was a preëxistent pathologic condition.

Strecker, Alpers, Flaherty and Hughes<sup>23</sup> gave metrazol to 7 monkeys in doses comparable to those usually given to human beings in the treatment of schizophrenia. Three animals did not exhibit any changes; 1 animal showed swelling and vacuolation of nerve cells in the upper cortical layers; 3 other animals showed slight subarachnoid hemorrhages. In the last-mentioned animals the cortex was remarkably well preserved. There were only a few slight changes in the cells of Betz, in the supraoptic nucleus and in the hypothalamus. But "this damage was never severe and may have no significance." The pathologic changes were seen only in animals in which the total convulsive time had been especially long (67 to 147 minutes).

Dreszer and Scholz<sup>4</sup> recently published the results of studies dealing with disturbances in the cerebral blood supply in generalized convulsions. They examined the brains of several cats in which convulsions had been provoked by cardiazol. The histologic work was based upon the benzidine method, which shows the distribution

of blood in the brain by the staining of the red blood cells. The authors found a definite disturbance in the capillary blood supply in the cortex in the preparoxysmal stage: there was a generalized capillary anemia together with numerous, variably-sized, circumscribed areas of more pronounced anemia. The anemia gave way to a hyperemia which began at the climax of the tonic phase of the convulsion and involved most of the vascular system during the clonic phase. The hyperemia, however, was not uniformly distributed; some anemic regions persisted at the end of the attack. A breaking-up of the blood columns into many small fragments was frequently seen in capillaries in regions originally not entirely anemic. The authors considered this to be evidence of a mild degree of capillary spasm which varied considerably throughout the anemic regions. The caliber of the large arteries seemed not to be altered. Dreszer and Scholz concluded that vasomotor disturbances play an important rôle in the causation of convulsions in experimental animals as well as in human beings.

Subsequent to convulsions induced by various means, acute destructive changes in the cortex have been described by Husler and Spatz,<sup>12</sup> von Braunmühl,<sup>1</sup> Scholz,<sup>20</sup> and by Neubürger.<sup>17a</sup> The shape of such cellular destructive changes corresponds closely to the areas of circumscribed capillary anemia occurring in the cat after convulsions induced by metrazol. Since such a marked disturbance in the blood supply follows metrazol injection, it may be assumed that pathologic changes in the nervous parenchyma are likely to result. Our histologic studies suggest this probability.

**Procedure.** Three dogs and 4 rabbits were given a series of convulsant doses of metrazol. The number of injections was similar to that employed clinically in the convulsive treatment of schizophrenia. The drug was given 3 times a week for a total of 14 to 18 injections. Most of the injections were given intravenously except in Rabbit 1, in which approximately one-half the injections were given intramuscularly or subcutaneously. It was frequently found necessary to increase the dose somewhat in order to maintain pronounced convulsive responses at approximately the same level. For the dogs the dosage varied from 10 to 35 mg. per kg.; for the rabbits it varied from 10 to 30 mg. per kg. These amounts are to be compared with a dosage of from 5 to 7 mg. per kg. employed in convulsive therapy in human beings. Six of the animals were killed by decapitation during the tonic stage of convulsions. One rabbit was permitted to survive the convulsions for 1 month before decapitation.

**Discussion.** Contrary to the findings of certain other investigators previously mentioned, we have observed that convulsant doses of metrazol given to dogs and rabbits may lead to organic pathologic changes. In the present study, the most important pathologic changes were observed in the central nervous system, especially the cerebral cortex (Figs. 1, 2, 3). More or less complete necrosis of the nervous parenchyma was observed in circumscribed areas; this was occasionally associated with slight glial reaction. In addition, there were diffuse degenerative changes of moderate degree in the

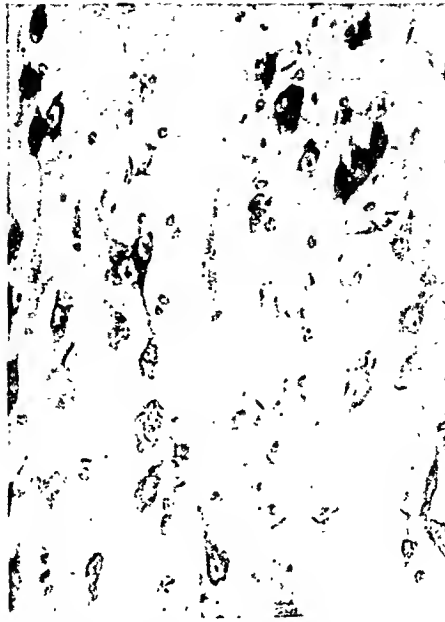


FIG. 1.—Area of recent ischemic necrosis in frontal cortex from Dog 3 which received 11 convulsant doses of metrazol. (Nissl  $\times 300$ .)

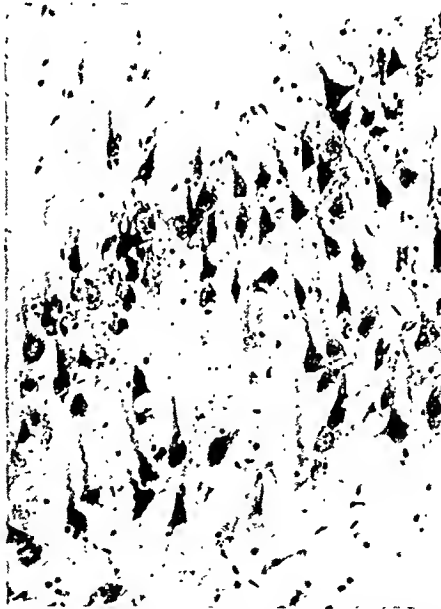


FIG. 2.—Circumscribed area of recent ischemic necrosis in hippocampus, showing slightly more pronounced changes than Figure 1 from Dog 3 which received 11 convulsant doses of metrazol. (Nissl  $\times 175$ .)

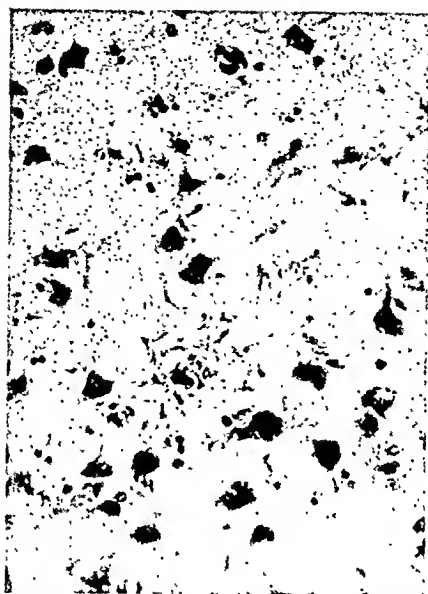


FIG. 3.—Neuronophagia in thalamus: proliferated glia cells surrounding a degenerating nerve cell, from Dog 3 which received 11 convulsant doses of metrazol (Nissl  $\times 300$ .)



FIG. 4.—Area of pronounced anemia in frontal cortex showing breaking-up of blood column in capillaries, from Dog 1 which received 14 convulsant doses of metrazol. (Benzidine stain [method of Doherty, Suh and Alexander<sup>3</sup>]  $\times 125$ .)

TABLE 1.—TABULATION OF RESULTS.

Protocol No.	Animal.		Experiment.			Dosage of metrazol.		Convulsive seizures.		Histologic findings at autopsy.			
	Sex.	Wt., kg.	Duration, days.	Injections.	Convulsant doses.	Range, mg. per kg.	Minimal convulsant dose, mg. per kg.	Num-ber.	Dura-tion.				
1 (Dog 1)	M	28.5	45	18	14	10-25	10	14	15 sec.-3 min.	Brain.  Degenerative nerve cell changes in cortex: vacuolation, paleness, indistinct nuclear boundaries and very small nucleoli. In some areas of lower cortex: neuronophagia, "shadow" nerve cells, rod cells and slight proliferation of protoplasmic astrocytes. Some hyalinization in precapillary walls. (See also results of benzidine method in Discussion.) Changes similar in type and degree to those described in Protocol 1.	Lungs. Congestion; hemorrhages; atelectasis	Other organs. Spleen. Congestion	Kidneys. Congestion; tubular degeneration
2 (Dog 2)	F	9.0	45	17	16	15-30	15	16	30 sec.-3 min.	Pathologic changes most pronounced in series. In areas of cortex, hippocampus and thalamus: ischemic and "severe" nerve cell changes, pyknosis and ameboid glia cells. Generalized degenerative changes in gray matter: dislocation of cells, disappearance of Nissl bodies, vacuolation of cytoplasm, large pale nuclei with darkly stained chromatin particles, swollen and tortuous processes. Glial proliferation as in Protocol 1. Slight hyperemia. Endothelial proliferation in some cortical capillaries. Slight hyalinization of walls of a few cortical and meningeal arterioles and precapillaries.	Congestion; hemorrhages (passive); atelectasis Congestion; hemorrhages	Congestion; hemosiderosis	Congestion; tubular degeneration.
3 (Dog 3)	F	12.8	51	19	11	12-35	25	11	30 sec.-7 min.	Pathologic changes less numerous and less conspicuous than in dogs. Scattered nerve cell changes: tigrolysis, sclerosis with tortuous dendrites, paleness, vacuolation, formation of intracellular rings (Nissl's "severe" change). Increased numbers of satellites, formation of "gliarosen." Some vascular dilatation.	Congestion (slight); atelectasis	Congestion (slight)	Congestion (slight); tubular degeneration.
4 (Rabbit 1)	M	4.0	49	17	8	10-20	10	8	1 min.-1½ min.	In some areas of lower cortex: paleness and disappearance of nerve cells, neuronophagia. Proliferation of protoplasmic astrocytes.	Congestion; hemorrhages; atelectasis	Congestion	Congestion; tubular degeneration.
5 (Rabbit 2)	M	2.62	45	15	11	10-30	15	11	45 sec.-3 min.	Pathologic changes less marked. Scattered nerve cell changes: paleness and vacuolation of cytoplasm, slightly increased prominence of dendrites. Glial proliferation as in Protocol 5.	Congestion; hemorrhages; atelectasis	Congestion	Congestion; tubular degeneration.
6 (Rabbit 3)	M	2.50	45	14	11	10-30	15	11	25 sec.-2 min.	Pathologic changes more severe than in other rabbits. In areas of lower cortex: paleness and vacuolation of nerve cells, neuronophagia, even "severe" changes in a few cells. Glial proliferation as in Protocol 1. Moderate nerve cell changes throughout cortex. Slight hyalinization in vessel walls as in Protocol 1.	Congestion; hemorrhages; atelectasis	Congestion; hemosiderosis (slight)	Congestion; tubular degeneration.

\* Injection period.

† Recovery period.



nerve cells. Other changes observed consisted of slight tubular degeneration in the kidneys in all animals, scattered hemorrhages in the lungs, increased amounts of hemosiderin in the spleen, possibly increased amounts of glycogen in the liver and generalized visceral congestion.

In consideration of the nature of the above-mentioned lesions, one important factor in the pathogenesis appears to be a disturbance in the circulation. Further evidence confirming this view was obtained from the study of the brain of 1 dog (Dog 1) by means of the benzidine method.\* The animal was killed at the height of the tonic stage of convulsions. Study of the brain revealed a breaking-up of the closed capillary network into irregular fragments (Fig. 4). The column of blood within the vessels was frequently interrupted. There was a generalized anemia which was more pronounced in some areas than in others. In a few scattered places there was an increased amount of blood. These results are in agreement with the previous more comprehensive study conducted by Dreszer and Scholz,<sup>4</sup> who employed the benzidine method in cats: an angiospastic-ischemic process is operative at the beginning of the convulsions. We are not able to state definitely whether this capillary spasm *per se* or a consequent stasis provokes the destruction of nerve cells. Comparative analyses of sections prepared by the benzidine and Nissl techniques may prove helpful. In places there is histologic evidence of hyperemia but not of stasis. We feel certain, therefore, that spasm of the capillaries is the principal circulatory disturbance involved and that this may be mainly responsible for the more or less circumscribed necrobiosis of the parenchyma. Leibel and Hall<sup>14</sup> have determined by direct measurement that during metrazol shock there is a decrease in cerebral blood flow, both arterial and venous, which is sufficient to produce a prolonged and severe cerebral anemia.†

In addition to the vascular disturbance another factor, anoxemia, appears to be operative in the pathogenesis of the lesions observed in the nerve cells. That metrazol convulsions produce considerable anoxemia is shown by the findings of Himwich and his co-workers,<sup>11</sup> who studied the blood changes during metrazol shock in human cases. During various stages of the convulsions the oxygen saturation of the blood fell to 42%. Even in the first moments after the convulsions ceased, the oxygen tension of the arterial blood did not reach the normal value. It is probable that the pathologic changes observed in the brain of the animals may, at least in part, be due to anoxemia. We may suppose that severe changes in the ganglion cells may arise at once incident to convulsions of 7 minutes' duration, as in Dog 3, and that convulsions of shorter duration, especially if

\* The modification of Doherty, Suh and Alexander<sup>3</sup> was employed.

† Metrazol exerts a profound influence upon the circulation (Hildebrandt [review],<sup>10</sup> McDonald and Cobb,<sup>15</sup> Haury and Gruber<sup>8</sup>).

frequently repeated, may lead to less severe changes which are perhaps partly reversible.

Recent work by Wortis<sup>24</sup> shows that metrazol has no effect on the respiration of brain tissue *in vitro*. His results suggest that the harmful effect which metrazol has been shown to exert on the tissues of the central nervous system, as determined in the present work, is probably not due to a direct toxic action.

In summary, we believe that the evidence permits the assumption that interference with the blood flow to the brain and the anoxemia produced by the convulsions are the essential factors in causing the cerebral changes.\*

The tissues of the rabbit which was allowed to survive 4 weeks after the last injection of metrazol did not exhibit any essential histologic differences from those of the other animals. There is no evidence of the formation of glia fibers nor of the production of scars. As yet, therefore, we are not able to say what becomes of foci of cellular destruction in the later stages. This rabbit, as well as Dogs 1 and 3, exhibited a very slight hyaline degeneration in the small cortical and pial vessels (arterioles and precapillaries). It may be assumed that repeated functional disturbances may favor the development of such changes in small vessels.

The true clinical significance of the brain changes observed in these experiments is not yet clear. The bulk of the nervous tissue appeared quite well preserved. The animals did not exhibit symptoms which could be referred to the brain changes.

The following clinical case shows correlative changes. A 26-year-old white male, who had received insulin-metrazol shock treatment for schizophrenia, made a fair recovery from his mental ailment but developed acute appendicitis which required operation. Post-operatively his condition was good and his temperature was normal. However, 2 months after the last injection of metrazol and 14 days after the last injection of insulin, the man suddenly died on the seventh postoperative day. At autopsy, 14 hours postmortem, death was shown to be due to pulmonary embolism incident to venous femoral thrombosis. Alterations in the brain were similar to those seen in the animals. The histologic findings were paleness and degeneration of scattered nerve cells and disappearance of a few cells in the hippocampus and neuronophagia in several cells, slight glial reaction and small "gliarosen" in the temporal cortex. Similar but less marked changes were observed in the frontal cortex, thalamus and interbrain. In places there was a slightly increased number of nuclei in the capillaries.

A second case of schizophrenia, in which convulsive metrazol therapy had been instituted, showed pathologic changes in the brain very similar to those mentioned in the above case. A 42-year-old

\* Recent literature relating to the effects of anoxemia on the brain may be found in the work of Dellaporta,<sup>2</sup> Kabat and Dennis<sup>13</sup> and Gamper and Stiefler.<sup>7</sup>

white male died 15 days after the third injection of metrazol. Death occurred as a result of pyemia secondary to a left perirenal abscess for which nephrectomy had been performed 14 days previously. The brain changes observed were different from those usually found in pyemic conditions. Therefore, we believe these changes to be due to the action of metrazol.

In many other conditions, such as hypertension and epilepsy, similar small areas of cellular destruction have been observed frequently in different regions of the brain of patients, who during life presented no symptoms referable to these lesions.

In contrast to these observations, other studies indicate that metrazol shock therapy is not always without harm. A recent report indicates that this therapy may produce memory defects, especially for "neural patterns" of recent origin (Ziskind and Somerfeld-Ziskind<sup>25</sup>). This fact should enjoin caution in its use. It is known that individual patients may be highly susceptible to the convulsive action of metrazol. Therefore, care should be exercised in the institution of such therapy. It is probable that severe and irreversible changes in the brain may result from the administration of the usual metrazol dose to such individuals. Recently another and more serious danger has been shown to accompany metrazol shock treatment. When metrazol shock therapy was first introduced, dislocations were found to be a frequent accompaniment of the convulsions. Fractures including those of the bodies of the thoracic vertebræ have been described recently.<sup>18</sup> It seems quite probable that these serious accompaniments of the treatment will necessitate modification of metrazol treatment or substitution of some other less drastic form of therapy. A report indicating that metrazol therapy should probably not be used in individuals with cardiac disease has been mentioned previously (Hayman and Brody<sup>9</sup>). The employment of convulsive therapy in these patients may result in sudden death. Other toxic effects involve the hemopoietic system. Fatal aplastic anemia has been reported to follow metrazol shock therapy.<sup>5</sup>

Certain pathologic findings in organs other than the brain deserve comment. The hemorrhages in the lungs appear to be secondary to the convulsions. The presence of increased amounts of hemosiderin in the spleen suggests that hemorrhages may have occurred in previous convulsive attacks. In some cases of death in human beings during epileptic convulsions pulmonary hemorrhages have been observed by Neubürger<sup>17b</sup> and others. The slight degree of nephrosis is probably transient; the pathogenesis of this nephrosis is open to question.

**Summary and Conclusions.** Repeated administration of convulsant doses of metrazol to dogs and rabbits may lead to organic pathologic changes. The most important lesions were noted in the central nervous system, especially in the cerebral cortex. More or less complete necrosis of the nervous parenchyma was observed in

small circumscribed areas. This was occasionally associated with slight glial reaction and with diffuse degenerative change of moderate degree in the nerve cells. Other changes observed consisted of a mild degree of tubular degeneration in the kidneys, scattered hemorrhages in the lungs, increased amounts of hemosiderin in the spleen and generalized visceral congestion.

The possible etiology of the pathologic changes in the brain is discussed. Vascular spasm causing insufficient blood supply and anoxemia resulting from the convulsions are regarded as fundamental in the pathogenesis of the lesions produced by convulsant doses of metrazol.

Since this paper was submitted for publication, two articles dealing with brain changes following metrazol have come to our attention: Hassin, G. B.: *Arch. Neurol. and Psychiat.*, 42, 679, 1939; Liebert, E., and Weil, A.: *Ibid.* p. 690.

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### THE PRESSOR ACTION OF BENZEDRINE AND PAREDRIENE.\*

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BENZEDRINE and the closely related phenylpropylamines first attracted attention because of their ability to produce an increase in the blood pressure of experimental animals and in man.<sup>2,7,17,22</sup>

\* This research was aided by a grant from Smith, Kline & French Laboratories.

Since the clinical report of Prinzmetal and Bloomberg in 1935<sup>23</sup> on the value of benzedrine in the treatment of narcolepsy more interest has been directed to the cerebral effects of this compound, and there has been a tendency to attribute all of its actions to central nervous system stimulation. The recent work of Myerson and his associates<sup>20</sup> also suggested that, in contrast to epinephrine, the blood pressure raising effect of benzedrine is not due primarily to peripherally mediated vasoconstriction. Paredrine,<sup>1</sup> a drug closely related to benzedrine, has been introduced recently; studies on the mechanism of its pressor action are few in number.

In the present work an attempt has been made to establish the site of action of these drugs. Two types of studies have been made:

1. Studies in man designed to test the effects of benzedrine and paredrine in patients in whom a marked fall in blood pressure occurred as a result of vasomotor paralysis due to spinal anesthesia. In most of these studies paredrine was the drug used, since the cerebral stimulating effect of benzedrine was undesirable under such circumstances.

2. Experiments based on the sensitivity of the central vasomotor centers to changes in the blood carbon dioxide concentration. Dale and Evans<sup>10</sup> showed that the activity of the bulbar vasomotor centers depends on the concentration of carbon dioxide in the blood, higher concentrations increasing the activity of these centers, while lower concentrations decrease their activity. On the other hand, changes in arterial blood carbon dioxide concentration do not affect vasoconstriction caused by the direct action of a drug on the smooth muscle of the arterial wall.<sup>24a</sup> It was therefore felt that the presence or absence of changes in blood pressure in response to changes in arterial blood carbon dioxide concentration in subjects in whom vasoconstriction had been induced by the action of benzedrine or paredrine would serve to localize the site of action of these drugs.

**Methods.** In the 10 studies of the action of the drugs in patients under spinal anesthesia 10 mg. of benzedrine or paredrine was given intramuscularly. In many instances the patients were pulseless. These studies were made in the operating room with the coöperation of the surgical service on patients in whom the systolic blood pressure had fallen to 60 mm. of mercury or lower following the induction of spinal anesthesia for various major operations.

In the 10 hyperventilation experiments the drugs were given orally in 30 or 40 mg. doses after the subject had rested in bed until his blood pressure became stable. Voluntary slow deep respiration was begun after the blood pressure reached a fairly constant high level, and was continued for 15 minutes. Alveolar air samples were taken by the Haldane technique at the beginning and end of hyperventilation and the carbon dioxide content was determined with the Haldane gas analysis apparatus. Blood pressure measurements were made at 2-minute intervals by the auscultatory method; the blood pressure level was noted for at least 10 minutes after the conclusion of hyperventilation. The pulse was counted frequently throughout the experiments.

**Results.** In patients in whom spinal anesthesia caused vasomotor paralysis and a marked fall in blood pressure, paredrine in every

instance raised the blood pressure to or above the pre-anesthesia level (Table 1). Similar results were noted in another group of patients following the injection of benzedrine.

TABLE 1.—EFFECT OF PAREDRINE AND BENZEDRINE ON BLOOD PRESSURE AFTER SPINAL ANESTHESIA.

Case.	B.P. before anesthesia.	B.P. before paredrine.	B.P. after paredrine.
1 . . . . .	120/75	30/0	150/80
2 . . . . .	150/80	40/20	180/120
3 . . . . .	130/80	60/40	160/60
4 . . . . .	150/110	50/0	160/80
5 . . . . .	100/60	0	90/60
6 . . . . .	130/80	0	120/80
7 . . . . .	100/60	0	100/60
8 . . . . .	120/60	50/20	160/70
		B.P. before benzedrine.	B.P. after benzedrine.
9 . . . . .	110/70	50/30	120/60
10 . . . . .	100/60	40/0	100/60

No significant fall in blood pressure occurred during or after voluntary hyperventilation (Table 2). In all instances the alveolar carbon dioxide content, and hence the arterial carbon dioxide content, was much diminished; mild tetany as manifested by numbness of the face and hands and the appearance of Chvostek's and Trousseau's signs occurred in 5 of the 10 subjects. The rises in blood pressure which occurred during the course of hyperventilation in several of the subjects were apparently due to the drug action since the elevation persisted after the end of forced breathing.

**Discussion.** Increases in systolic and diastolic blood pressure of the degree observed in the experiments here reported (Table 1) are similar to those which occur in essential hypertension and are due to arteriolar constriction. There is no basis for the statement frequently made that increases in cardiac output, blood volume, or blood viscosity elevate the blood pressure significantly, for normal values for blood pressure obtain in patients with increased cardiac output due to anemia and pregnancy,<sup>12</sup> in patients or animals with increased blood volume due to intravenous infusions,<sup>4,26</sup> and in patients with polycythemia vera<sup>16</sup> in which the blood viscosity may be increased to three or four times the normal value.

The results of the present study, which show that the blood pressure may be elevated markedly by the administration of benzedrine and paredrine in patients with peripheral vasomotor paralysis due to spinal anesthesia, indicate that these drugs act on the blood-vessel walls. Similarly, the observations that these drugs produce local vasoconstriction when applied to mucous membranes,<sup>8</sup> that they cause contraction of isolated strips of smooth muscle,<sup>21</sup> and that they retard the flow of blood through isolated animal tissues<sup>14</sup> point to the peripheral arterioles as the site of action of these drugs. Complete destruction of the brain and spinal cord<sup>3</sup> or paralysis of the sympathetic ganglia by means of nicotine or sparteine<sup>27</sup> does

not prevent a rise in blood pressure after administration of these drugs in animals. The failure of paredrine to produce blanching and cooling of the skin such as occurs after the administration of adrenalin<sup>1</sup> is not necessarily evidence against the presence of vasoconstriction elsewhere. Indeed there are available data which prove that the action of adrenalin on the skin is not an accurate measure of what happens in the rest of the body.<sup>11</sup>

TABLE 2.—EFFECT OF HYPERVENTILATION ON HYPERTENSION INDUCED BY BENZEDRINE AND PAREDRIENE.

Patient.	Drug and dose.	Blood pressure.			Alveolar CO <sub>2</sub> (%).		Remarks.
		Basal.	Start of hyperventilation.	End of hyperventilation.	Start of hyperventilation.	End of hyperventilation.	
A. I. . .	30 mg. Benzedrine	120/78	154/98	156/96	5.17	2.73	Tetany
M. J. K.	30 mg. Benzedrine	104/60	136/84	138/84	5.03	2.60	Tetany
G. W. . .	30 mg. Benzedrine	110/68	146/84	146/90	5.74	3.47	
J. W.	30 mg. Benzedrine	108/60	140/78	148/88	5.10	2.87	Tetany
G. G.. .	30 mg. Benzedrine	98/68	146/78	150/80	5.12	3.05	
E. C. . .	30 mg. Benzedrine	92/72	132/80	128/86	5.23	2.12	Tetany
W. P. . .	40 mg. Paredrine	125/60	160/78	168/82	5.14	3.28	
G. H. . .	40 mg. Paredrine	118/68	144/78	154/86	5.36	3.68	
W. B. . .	40 mg. Paredrine	106/74	156/80	146/86	5.00	3.53	
M. D. A.	40 mg. Paredrine	110/74	154/88	176/90	5.31	2.53	Tetany

The experiments in which hyperventilation was employed contribute suggestive but not conclusive data as to the site of action of the drug. Dale and Evans<sup>10</sup> and Raab<sup>24b</sup> have shown in animals that the activity of the bulbar vasomotor centers varies as the concentration of carbon dioxide in the blood perfusing these centers. These observations have been utilized clinically by Raab<sup>24a</sup> to differentiate centrally from peripherally affected vasoconstriction. He showed that lowering the arterial blood carbon dioxide concentration by means of hyperventilation lowered the blood pressure markedly in patients with essential hypertension but not in patients

with nephritic hypertension or hypertension due to the injection of adrenalin, a drug which acts on the peripheral arteries. The converse has also been observed clinically; inhalation of 10 % carbon dioxide raises the blood pressure more markedly in patients with essential hypertension than in normal subjects.<sup>15</sup> Similarly, holding the breath, which has been shown to cause a rapid increase in alveolar carbon dioxide concentration,<sup>9</sup> raises the blood pressure of patients with essential hypertension to a greater degree than that of normal subjects.<sup>6</sup> Since, according to Raab,<sup>24a</sup> hyperventilation lowers the blood pressure in hypertension when it is due to centrally mediated vasoconstriction but not when it is due to peripherally mediated vasoconstriction, hyperventilation was considered an additional means of localizing the site of action of benzedrine and paredrine. The fact that hyperventilation to the point of tetany failed to lower the blood pressure after it had been elevated by the administration of these drugs, is additional evidence pointing toward its peripheral action.

A number of foreign investigators have contended that paredrinol (Veritol), a methyl derivative of paredrine, raises the blood pressure by constricting the veins,<sup>13,25,27</sup> thereby squeezing blood into the arterial portion of the circulation. Whether or not such constriction of the veins occurs is at present being investigated in this laboratory, but even if appreciable venous constriction does occur, the increase in blood pressure cannot be explained on this mechanism since temporary or persistent<sup>4,16</sup> increases in blood volume do not have this effect.

The absence of generalized evidences of sympathetic activity, such as increase in metabolism, rise in blood sugar, increase in cardiac output, constant rise in pulse rate after the administration of benzedrine or paredrine,<sup>5,18,19</sup> is additional evidence against occurrence of central sympathetic stimulation. Similarly, the differences in the duration and time of onset and offset of cerebral stimulation and of blood pressure rise after the administration of benzedrine point to different sites of action. Benzedrine may produce marked psychic effects in the absence of measurable cardiovascular changes, while paredrine causes marked increase in blood pressure without cerebral stimulation.

**Summary and Conclusions.** 1. The marked pressor action of benzedrine and paredrine is due to arteriolar vasoconstriction.

2. Benzedrine and paredrine exhibit their usual pressor effects in patients in whom the vasomotor nerves of most of the body have been paralyzed by means of intraspinal nupercaine or novocaine.

3. Hyperventilation with its resultant marked decrease in arterial blood carbon dioxide concentration does not inhibit the pressor action of these drugs.

4. These observations are in accord with other evidence indicating that the smooth muscle of the arterioles is the site of the pressor action of these drugs.



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## THE EFFECT OF SULFAPYRIDINE ALONE AND WITH SERUM ON PNEUMOCOCCIC PNEUMONIA AND ON PNEUMOCOCCUS-INFECTED MARROW CULTURES.\*

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A CONSIDERABLE body of evidence has accumulated to indicate that *in vitro* the bacteriostatic and bactericidal action of sulfapyridine against the pneumococci<sup>15a,21,24,28,37a</sup> is superior to that of sulfanilamide. It has, moreover, been shown that sulfapyridine is capable of prevent-

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ing or curing pneumococcal infections in a variety of animals, and that this action is superior to that of sulfanilamide.<sup>10,18,20,21,24,27,37a,33</sup> This knowledge has been employed in the treatment of human pneumococcal infections, and reports have appeared showing the value of sulfapyridine in the treatment of the pneumonias and of other infections caused by the pneumococcus.<sup>1-4,11-14,16,17,26,29,32,34-36,38</sup> A number of workers have reported that specific serum increases the antistreptococcal and antipneumococcal activity of sulfanilamide, both *in vitro* and in experimental infections.<sup>5,7,19,25,30</sup> There have been several reports suggesting that specific immune bodies increase the antipneumococcal activity of sulfapyridine.<sup>15a,28</sup>

An evaluation of serochemotherapeutic and chemotherapeutic methods, by clinical means alone, would require considerable numbers of cases and years of observation. Though the clinic is the ultimate arbiter, the problem may be simplified and its elements may be separately analyzed and evaluated by laboratory approach. The technique of vaccine vial culture of human marrow permits controlled quantitative studies of the interaction of living cells, bacteria and therapeutic agents. This has already been demonstrated for sulfanilamide, with both streptococci and pneumococci.<sup>30,31a,b</sup> The present work represents an extension of original observations to include sulfapyridine and attempts to evaluate the importance of adding specific serum.

**Method.** The method of vaccine vial culture of human marrow has already been described.<sup>31a</sup> Human marrow serum medium at a buffered pH was infected with organisms. Equal portions were introduced into vials. The serum and sulfapyridine was then introduced through the stopper. Portions for examination were aspirated from time to time. The organisms used in the present investigations were strains recently isolated from pneumococcal pneumonia patients. The blood of patients was obtained by sterile technique, allowed to clot, and the serum centrifuged sterilely and refrigerated.

**Results.** A. DIRECT EFFECT IN MARROW CULTURES. (a) *Effective Dosage; Comparison With Sulfanilamide.* The control observations evidenced the same characteristics already described for the growth of pneumococci in marrow cultures.<sup>30,31b</sup> The usual growth of the pneumococcus under the conditions studied is demonstrated in Exp. 221 (Chart 1), performed on a freshly isolated virulent Type VII pneumococcus. Though as small an inoculum of this strain as 68 organisms per cc. was not sterilized by sulfapyridine alone (Exp. 220), a larger inoculum, 470 organisms per cc., was completely sterilized in 70 hours by sulfapyridine 10 mg. per 100 cc. plus 5 units of antiserum per cc. Sulfanilamide, 1 to 10,000, was practically without effect. Our general experience was that for the same size inoculum, concentrations of sulfapyridine equi-molar with 1 to 10,000 or 1 to 20,000 sulfanilamide were effective and more so than sulfanilamide or than the lower concentrations of sulfapyridine.

Because these concentrations are significantly bacteriostatic in marrow cultures and because they can be reached in the blood of human subjects (5 and 10 mg. per 100 cc. of blood), they were employed in the subsequent experiments. The effective concentrations of sulfapyridine alone in marrow cultures corresponded well with the observations of other workers, but is somewhat higher than that previously described for sulfanilamide against the streptococcus. An apparently effective concentration may not control all pneumococci, since there may be considerable variation in susceptibility of different strains to sulfapyridine.

Acetyl sulfapyridine had neither bactericidal nor bacteriostatic effect.

EXP. 221  
JACKSON TYPE VII

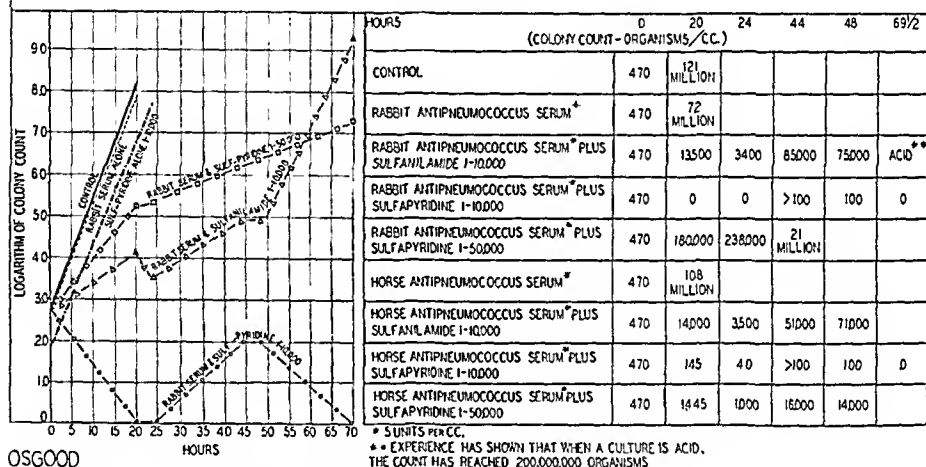


CHART 1.—Effect of sulfapyridine and sulfanilamide on *Pneumococcus* VII in marrow culture. Influence of added serum.

(b) *Lag Phenomenon.* In most of the experiments there was, immediately after inoculation, multiplication of the organisms for a period of several hours before bacteriostasis occurred (Charts 2 and 3). This phenomenon has been observed with sulfonamide compounds by several workers, particular reference having been called to it by Whitby.<sup>37b</sup>

(c) *The Effect of Type Specific Antibody.* The effect of both horse and rabbit sera on the bacteriostasis in marrow cultures containing sulfapyridine was studied. There was an equal effect for equivalent titers of antibody. The majority of our later experiments were performed with rabbit serum. Serum alone, in concentrations of 5 to 60 units per cc., induced, within the marrow culture, the usual specific phenomena of capsule swelling, agglutination and stimulation of phagocytosis. Serum alone had less effect on the growth

curves of the pneumococci than had been observed with the organisms used in the sulfanilamide experiments.<sup>30</sup> There was frequently diminished growth during the first 4 to 6 hours in the vials containing only specific serum, possibly due to agglutination (Chart 2), but this was generally followed by a rapid increase of growth, closely paralleling that of the control cultures.

In the majority of instances, bactericidal and bacteriostatic activity was appreciably increased when both serum and drug were present (Charts 1, 3 and 4-b). Where either very large or very

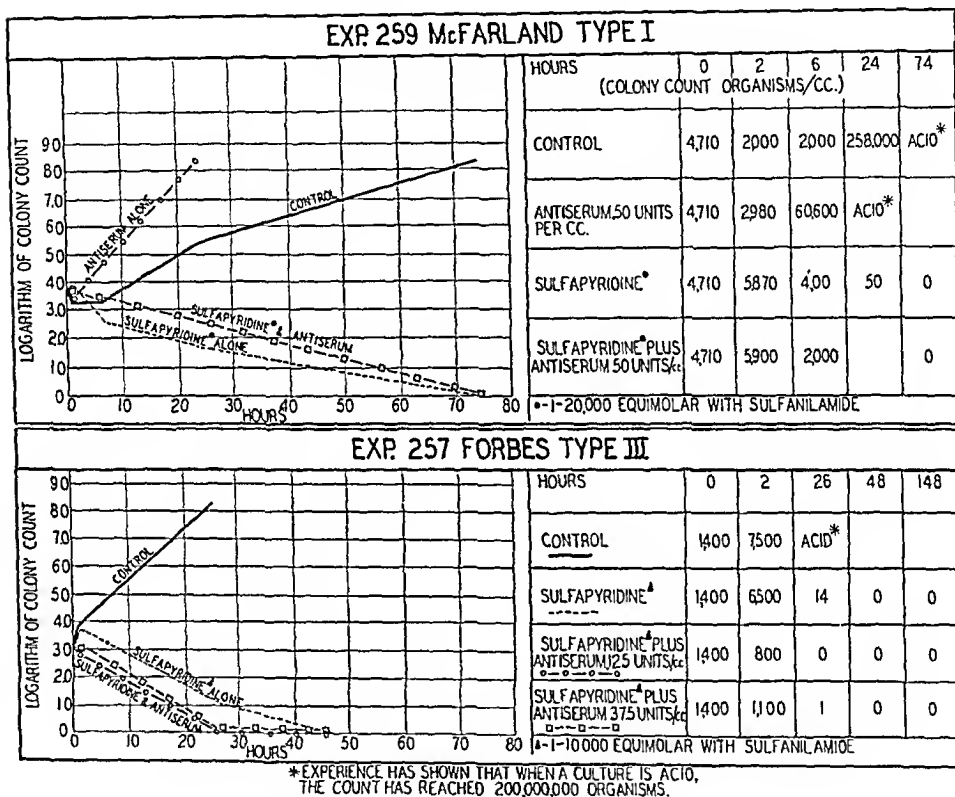
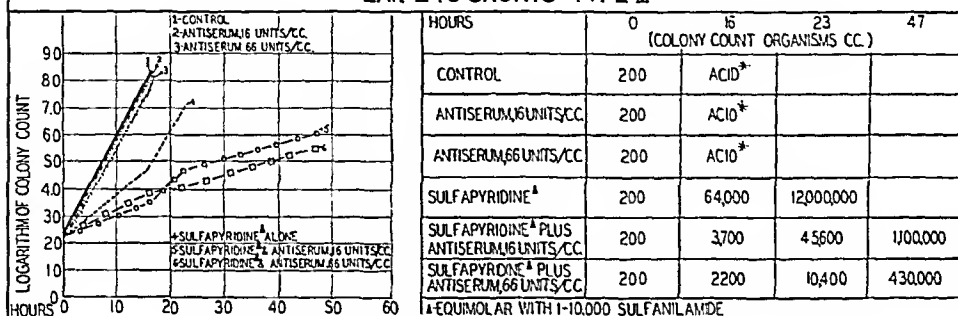


CHART 2.—(a) and (b). *Pneumococcus* I and *Pneumococcus* III in marrow cultures. Failure of serum to increase bacteriostatis.

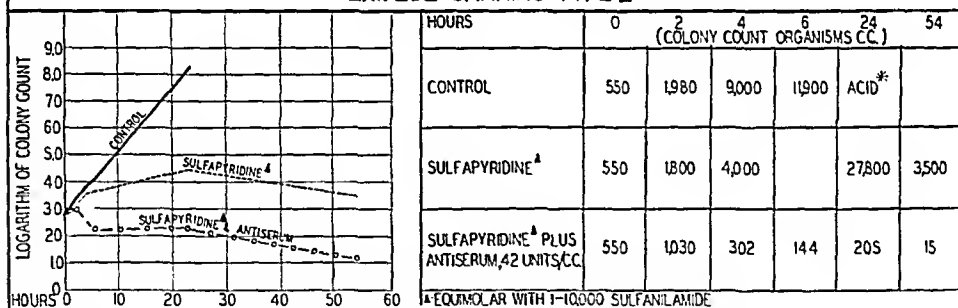
small inoculations were used, however, the effect was less evident because, with the smaller inoculations, sulfapyridine alone was effective and with the very large inoculations neither the drug alone nor in combination with serum was capable of controlling the infection. Occasionally, however (Chart 5-b), an inoculum as large as 30,000 organisms per cc. of pneumococcus III was completely sterilized in 96 hours by sulfapyridine plus serum although it was not sterilized by sulfapyridine alone. Of interest in Exp. 252 (Chart 3) was the demonstration that, in the vial containing sulfapyridine plus serum, there were still 15 viable organisms per cc. at 54 hours.

That small numbers of organisms may remain alive for a long time in the presence of both sulfapyridine and serum, is of considerable importance in determining therapy. In several experiments, increasing antibody concentrations with the same concentrations of sulfapyridine, gave evidence of increasing bacteriostatic effects (Chart 3-a). This was not in proportion to the increase of antibody. Rarely the presence of antiserum inhibited the bacteriostatic activity of the sulfapyridine.

## EXP. 248 SHORTS TYPE I



## EXP. 252 CANNING TYPE I



\* EXPERIENCE HAS SHOWN THAT WHEN A CULTURE IS ACID, THE COUNT HAS REACHED 200,000,000 ORGANISMS.

CHART 3.—(a) and (b). Two strains of *Pneumococcus* I showing increased susceptibility to sulfapyridine in the presence of serum.

(d) *The Effect of Variation in Virulence.* Experiments 221, 223, 227 and 228 (Chart 6) were performed with the same strain of a Type VII organism. Approximately 4 weeks elapsed between the first and last observations, during which time the organism had been subcultured on blood agar slants. A progressive increase in the organisms' susceptibility took place, and in later experiments (228), large inoculations were completely sterilized by concentrations of sulfapyridine alone which had failed in the first experiments. Moreover, in the initial experiment (Chart 1) antiserum in addition had been necessary to sterilize. Suspensions containing 10,000 organisms in the stage used in Exp. 228 were unable to kill mice. For this organism at least, the increased vulnerability to the drug

was associated with a considerable decrease in virulence for mice. These observations indicate that firm conclusions must not be based upon comparisons involved in a single experiment, and, when several experiments are considered, the inferences can be only tentative.

(e) *Strain Variations.* The existence of variations in susceptibility to sulfapyridine, already indicated, suggests the possibility that there might also be variations among different strains of the same type of organism in the same stage of isolation. The following comparative observations were not made simultaneously and, while

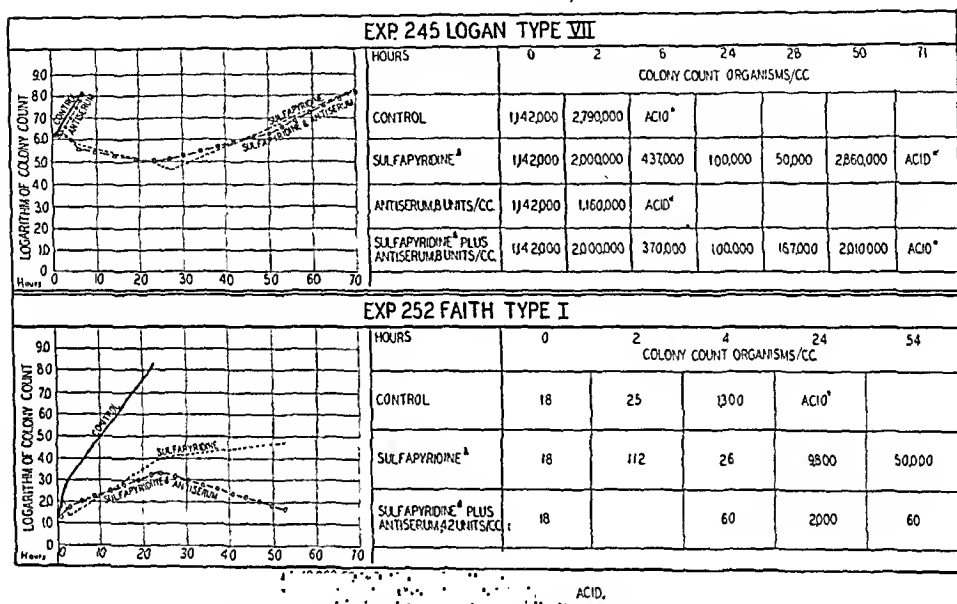


CHART 4.—(a) Large inoculum of *Pneumococcus* VII showing temporary bacteriostasis and later growth. (b) Failure of sulfapyridine to sterilize small inoculum despite added *Pneumococcus* I serum.

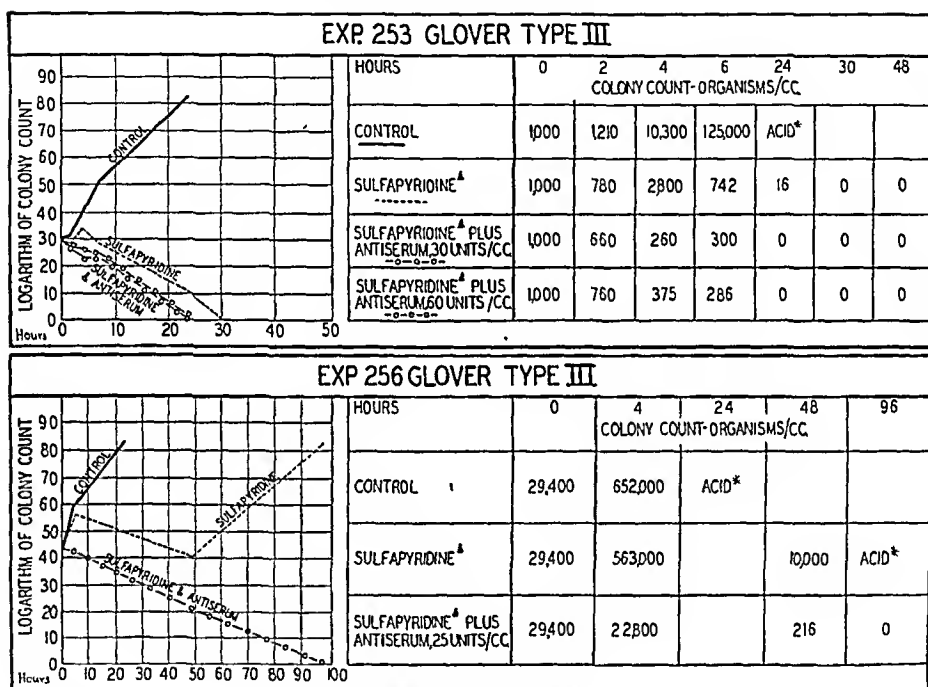
conclusions based upon them must be guarded, we may, nevertheless, tentatively accept that there are variations in susceptibility of different strains of pneumococci to sulfapyridine. The recent observations of MacLean, Rogers and Fleming<sup>28</sup> support this view.

A Type I strain (Faith) could not be sterilized in an inoculum of only 18 organisms per cc. by sulfapyridine and serum in 54 hours (Chart 4). Another Type I strain (Garret), in an inoculum of 700 organisms per cc., was completely sterilized by sulfapyridine alone in less than 74 hours.

(f) *Effect of Size of Inoculum.* That the size of the original inoculum is an important factor in determining the outcome of an experiment, is indicated in Chart 5. One thousand organisms per cc. of a Type III strain (Glover) were sterilized by sulfapyridine alone in 30 hours, while 30,000 organisms of the same strain in a later experiment could be sterilized only by sulfapyridine and serum after

96 hours. This would tend to show that concentrations of sulfapyridine which are perfectly adequate for smaller inocula of some strains may be inadequate when larger inoculations of the same strain are used.

With extremely large inocula (which were made to assure a sufficient growth so that adequate morphologic observations could be made) it was interesting to note that temporary bacteriostasis might occur, only to be followed by ultimate growth of the marrow culture to acidity (Chart 4-a). These observations are in agreement with the quantitative studies of McIntosh and Whitby,<sup>27</sup>



<sup>†</sup>-1:10000 EQUI-MOLAR WITH SULFANILAMIDE

\*-ACID-200,000,000 ORGANISMS

CHART 5.—(a) Successful sterilization of moderate inoculum (1000 organisms per cc.). (b) Very large inoculum (29,400 organisms) successfully sterilized only after serum was added.

who demonstrated the necessity of increasing concentrations of sulfapyridine for the sterilization of larger inocula of the same organism. The relationship in our experiments, however, did not seem to have the direct proportions of a quantitative chemical reaction.

**B. EFFECT OF VARIATIONS IN THE MEDIUM.** The influence of variations in the culture medium on the bacteriostatic and bactericidal action of sulfapyridine has attracted considerable attention. This, like the lag phenomenon, bears upon the highly important problem of the mechanism of action of the drug. We failed to

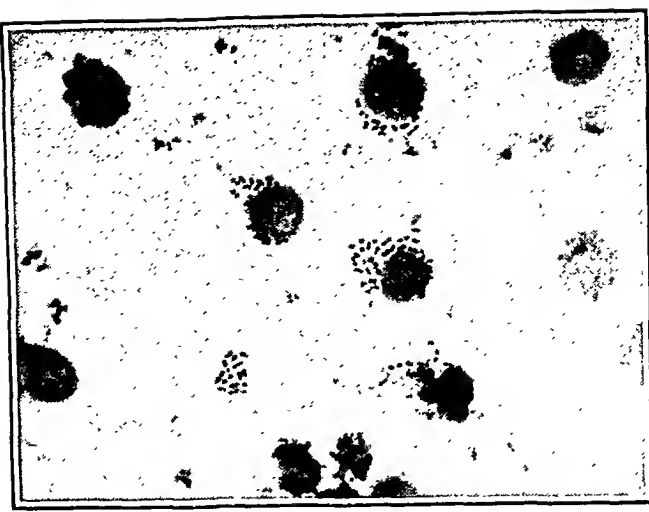


FIG. 1a.—Exp. 258. *Pneumococcus* VII. Control at 24 hours. (Wright stain smear from marrow cultures,  $\times 1200$ .) (Courtesy of Spencer Lens Company.)



FIG. 1b.—Exp. 258. *Pneumococcus* VII. Sulfapyridine, 1 to 20,000 at 24 hours. Lysis, chain formation phagocytosis.



FIG. 1c.—Exp. 248. *Pneumococcus* I. Sulfapyridine, 1 to 10,000 plus 66 units serum per cc., 16 hours. Distortion, lysis and chain formation.





FIG. 1d.—Exp. 258. *Pneumococcus* VII. Sulfapyridine, 1 to 20,000, plus anti-serum, 50 units per cc., 24 hours. Lysis distortion and chain formation.



FIG. 1e.—Exp. 258. *Pneumococcus* VII. Antiserum, 50 units per cc., 24 hours. Agglutination and capsule swelling.

observe inhibition of bacteriostasis due to added peptone, as reported by Lockwood. Our experience is in agreement with the observations of McIntosh and Whitby.<sup>27</sup> Phagocytosis was apparently not essential in determining the outcome of therapy because sulfapyridine accomplished complete sterilization of pneumococci inoculated into Hartley broth.

C. MORPHOLOGIC CHANGES UNDER INFLUENCE OF DRUG AND SERUM. 1. *In Marrow Culture*. Marked morphologic changes in streptococci exposed to sulfanilamide have been observed.<sup>7,23</sup> A

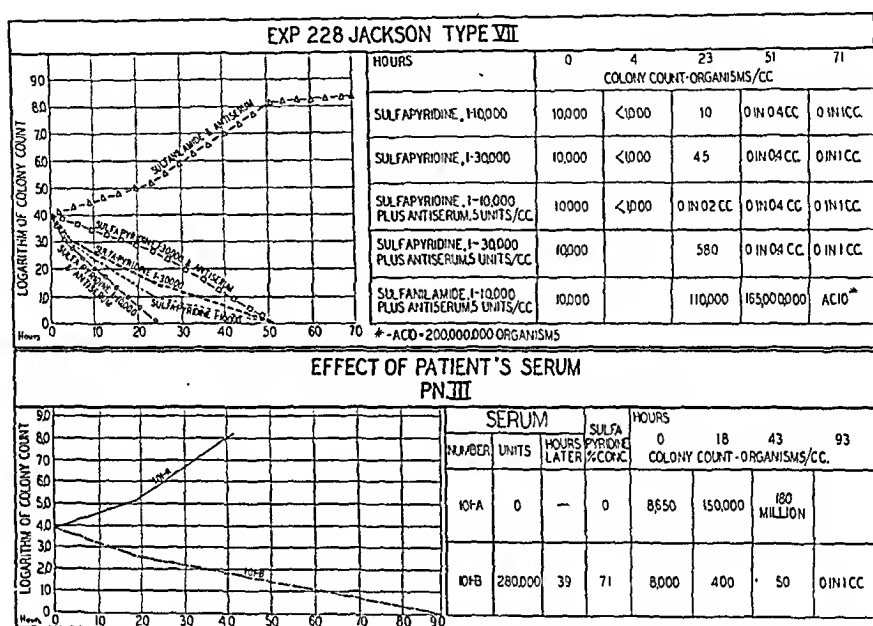


CHART 6.—(a) Increased vulnerability of *Pneumococcus* VII, same strain as in Exp. 221, after 1 month's cultivation in agar. (b) Exp. 220. Effect of patient's serum before and after treatment with serum and sulfapyridine.

report has appeared ascribing to sulfapyridine, morphologic alterations in the pneumococci obtained from treated patients.<sup>36</sup> Loss of capsular substance with a consequent loss of type specificity has been described. This has not, however, been confirmed by others so that doubt has been thrown upon the observations.<sup>15b, 21, 28</sup>

In our study of morphologic changes in marrow cultures, large inocula were made and Wright stain smears examined at various intervals (Fig. 1-a, b, c, d and e). In general, morphologic alterations were observed after some hours of exposure to the drug. These changes consisted of a tendency to chain formation, swelling and distortion of the organisms, and actual lysis. In the presence of specific antiserum capsule swelling occurred. Agglutination of organisms also occurred when antiserum was present, indicating that type specificity was retained. At the same time, the control cultures, with more bacteria than those containing sulfapyridine,

showed good morphology, indicating that the morphologic changes were not due either to exhaustion of the media or to the production of metabolites. Phagocytosis also was not responsible for morphologic changes because it was present in the control cultures to the same degree as in cultures containing the drug.

2. *In Patients.* In a number of instances, sputa from pneumonia patients treated with sulfapyridine were typed at intervals during the course of treatment. We were always able to obtain the type

### PN. I INFECTED MARROW CULTURE EFFECT OF PATIENT'S SERUM

PATIENT	SERUM		SULFA-PYRIDINE % CONC	HOURS					
	UNITS	HOURS LATER		0	17	21	41	45½	92
ORGANISMS/CC (COLONY COUNT)									
107-A	0	—	6.0	A) 10	2			148	100,000,000
				B) 17,700		<100,000,000			
142-A	0	—	6.7	A) 5	0			0	0
				B) 17,700		200,000,000	<400,000,000		
102-A	420,000	36	80	A) 10	0			0	0
				B) 17,700		80,000	<100,000,000		
143-A	156,000	36	83	A) 5	0			0	0
				B) 17,700		40,000	600,000		<100,000,000

OSGOOD

A-WASHINGTON PN.I CULTURE  
B-VARGAS PN.I CULTURE

CHART 7.—Relative bactericidal activity of serums from treated patients.

from these sputa, either by direct examination (Neufeld), or by mouse inoculation. In 1 instance of Type VIII pneumonia, pneumococci continued to be typed directly from the sputum for 8 successive days of treatment with sulfapyridine. This patient recovered. In a fatal pneumococcal Type XVIII meningitis treated with sulfapyridine and both intravenous and intrathecal specific antiserum, capsules were seen on direct examination of the spinal fluid without addition of typing serum, for a period of 5 days;

throughout all of this time the spinal fluid concentration of sulfapyridine ranged between 5 and 9 mg. per 100 cc.

D. RELATIVE ANTIBACTERIAL POWER OF BLOOD OBTAINED FROM PATIENTS. Colebrook, Buttle and O'Meara<sup>9</sup> have demonstrated that treatment with sulfanilamide confers increased bactericidal and bacteriostatic properties upon the blood and serum of humans. Fleming<sup>15b</sup> demonstrated this phenomenon with human blood obtained from patients receiving sulfapyridine, and showed that the increased bactericidal property was in the serum rather than in the cells. We studied the bactericidal property of 10 specimens of human serum obtained from patients of several types, in some cases before treatment, but in most instances after treatment with either serum, sulfapyridine, or the combination. These sets of sera were subjected to studies in marrow cultures at the same time, using the same organism and, whenever possible, the same size inoculum. Although we did not determine the relative bactericidal power of normal human sera in marrow cultures, Colebrook, Buttle and O'Meara<sup>9</sup> have already shown that, although human whole bloods from various individuals differ in their bactericidal action against the streptococcus, there was practically no variation when only serum was used.

The serum of patients treated with sulfapyridine was considerably less bacteriostatic than the serum from those patients treated with both serum and sulfapyridine. Serum from patients given therapeutic serum alone had practically no bacteriostatic activity. Serum from untreated patients exhibited no significant bacteriostatic or bactericidal activity. Experiment 220 (Chart 6) clearly demonstrates the difference in sera obtained from a Type III patient before treatment and after treatment with both serum and sulfapyridine. Chart 7 demonstrates the same phenomenon with different sizes of inocula. There was increased bactericidal activity in the presence of both serum and drug.\*

E. STATISTICAL RESULTS OF THERAPY IN HUMAN INFECTIONS. During the past 4 months we have rotated in treatment patients with pneumococcic pneumonias, immediately after type identification, in order to evaluate the effect of serum, sulfapyridine, or the combination; 324 adults and 113 children were studied, as shown in the tables 1, 2, 3.

\* Since this article went to press, Spring, Lowell and Finland (J. Clin. Invest., 19, 163, 1940) have reported observations on the effect of sulfapyridine on the growth curve of the pneumococcus *in vitro*. Their studies also revealed the presence of a lag phase before bacteriostasis due to sulfapyridine, diminishing bacteriostatic effect with increasing size of inoculum, and a failure of peptone to inhibit bacteriostasis due to sulfapyridine. In their pneumococcal studies the addition of specific immune serum was also found to increase the bacteriostatic and bactericidal activity of sulfapyridine. They obtained results essentially similar to ours in studies of the pneumococcal activity of bloods obtained from treated patients, concluding that the pneumococcal activity was proportional to the sulfapyridine and antibody content of the blood specimens obtained.

The death rate in adults, for all types, with sulfapyridine alone, was significantly lower than that for serum alone. Curiously, the death rate with serum plus sulfapyridine was somewhat higher than that for the drug alone. This is at variance with the experimental results reported by others and with our own observations in marrow cultures. However, when the statistics are broken down, it becomes evident that the lowest death rate in early treated cases (1 to 4 days) was obtained with the combination of serum and sulfapyri-

TABLE 1.—NEW YORK UNIVERSITY COLLEGE OF MEDICINE (LITTAUER FUND), HARLEM HOSPITAL, JANUARY 1, 1939–MAY 1, 1939.

ADULTS.

Type.	Serum.			Sulfapyridine.			Serum and sulfapyridine.		
	Cases.	Deaths.	%.	Cases.	Deaths.	%.	Cases.	Deaths.	%.
I . . .	25 4*	1 0*		24 7*	0 0*		20 2*	1 0*	
II . . .	4 1*	0 0*		2 0*	1 0*		2 1*	0 0*	
III . . .	11 2*	4 2*		12 1*	1 1*		10 2*	2 2*	
V . . .	10 0*	1 0*		10 4*	3 3*		8 1*	1† 1*	
VII . . .	18 4*	5 3*		18 1*	0 0*		18 1*	2 1*	
VIII . . .	7 2*	1 0*		7 2*	1 1*		5 0*	1 0*	
Other types‡	36 4*	7 3*		52 1*	4§ 0*		26 1*	3 1*	
Total . .	111 17*	19 8*	17.3 47*	124 16*	10 5*	8.1 31*	89 8*	10 5*	11.2 62.5*

R.D.E. = 2.1

R.D.E. = 0.7

R.D.E. = 1.2

\* Bacteremia.

† Bacteremia controlled, congestive failure.

‡ Including multiple infections.

§ Pneumonia controlled, gastro-intestinal malignancy (1 case).

dine. These findings are in agreement with the recent experimental observations of Kepl and Gunn<sup>22</sup> on rats. They found that serum plus sulfapyridine was the most efficient therapeutic agent when treatment was begun soon after infection, and that in animals treated late the addition of serum did not augment the therapeutic effects obtained with sulfapyridine.

Final conclusions regarding the effect of drug and antibody in the treatment of the pneumonias must await additional observations.

**Comments and Discussion.** Most of the work done on sulfanilamide and its derivatives has, for its goal, the establishment of a rational therapy. In this regard, we have reason to believe that the same principles which govern the therapy of streptococcal infections with sulfanilamide will also govern the therapy of pneumococcal infections with sulfapyridine. It has been well established that specific serum markedly improves the sulfanilamide therapy of

TABLE 2.—NEW YORK UNIVERSITY COLLEGE OF MEDICINE (LITTAUER FUND), HARLEM HOSPITAL, JANUARY 1, 1939–MAY 1, 1939.  
CHILDREN.

	Serum.			Sulfapyridine.			Serum and sulfapyridine.		
	Cases.	Deaths.	%.	Cases.	Deaths.	%.	Cases.	Deaths.	%.
Total . .	37 4*	1 0*	2.7 0.0*	50 0*	2 0*	4.0 0.0*	26 1*	1 0*	3.8 0.0*
Age.									
Under 2 yrs.	17 3*	1 0*	5.9 0.0*	22 0*	2 0*	9.1 0.0*	13 1*	1 0*	7.7 0.0*
2 to 12 yrs.	20 1*	0 0*	0.0 0.0*	28 0*	0 0*	0.0 0.0*	13 0*	0 0*	0.0 0.0*
Pn. XIV .	11 3*	0 0*	0.0 0.0*	10 0*	0 0*	0.0 0.0*	11 1*	0 0*	0.0 0.0*
Lobar . .	32 4*	1 0*	3.1 0.0*	42 0*	0 0*	0.0 0.0*	25 1*	1 0*	4.0 0.0*
Broncho. .	5 0*	0 0*	0.0 0.0*	8 0*	2 0*	25.0 0.0*	1 0*	0 0*	0.0 0.0*

\* Bacteremia.

experimental infections. Lowenthal<sup>25</sup> found that serum plus sulfanilamide cured 75% of mice infected with streptococci while sulfanilamide alone cured 11% and serum alone cured none. Branham and Rosenthal<sup>5</sup> similarly found that the recovery rate for serum plus sulfanilamide in experimental pneumococcus infections was greater than for either alone and could not be accounted for by a simple addition of effects. Chandler and Janeway<sup>7</sup> demonstrated *in vitro* an increased bacteriostasis of the streptococcus by sulfanilamide in the presence of immune serum. MacLean, Rogers and Fleming<sup>28</sup> have shown that a single dose of pneumococcal vaccine combined with the oral administration of sulfapyridine saved mice that would inevitably have died if treated by either method alone; this was ascribed to the synergistic action of vaccine and drug. Agranat, Dreosti and Ordman<sup>1</sup> demonstrated that the

recovery from pneumonia occurred more quickly with sulfapyridine in those natives who had previously been vaccinated with pneumococci. Plummer and Ensworth<sup>32</sup> reported a mortality rate in cases treated with sulfapyridine and serum lower than that for sulfapyridine alone. Our observations also indicate that serum plus sulfapyridine is a more effective therapeutic agent than either acting alone in the early cases when autogenous antibody cannot be expected to be present. Furthermore, Bukantz, Bullowa and de Gara<sup>6</sup> have recently suggested that serum plus sulfapyridine may be essential when the severity of a pneumococcal infection is so great that capsular polysaccharide is detected in the blood.

TABLE 3.—NEW YORK UNIVERSITY COLLEGE OF MEDICINE (LITTAUER FUND), HARLEM HOSPITAL, JANUARY 1, 1939–MAY 1, 1939.  
ADULTS.

Age.	Serum.			Sulfapyridine.			Serum and sulfapyridine.		
	Cases.	Deaths.	%.	Cases.	Deaths.	%.	Cases.	Deaths.	%.
Under 40 yrs.	61 8*	8 3*	13.1 37.5*	72 9*	4 2*	5.6 22.2*	52 3*	3 1*	5.8 33.3*
				R.D.E. = 1.5					
40 years and over	49 9*	11 5*	22.5 55.7*	52 7*	6 3*	11.5 43.0*	37 5*	7 4*	19.0 80.0*
				R.D.E. = 1.5					
Day of disease: 1st to 4th day	57 9*	7 4*	12.3 44.5*	53 5*	5 2*	9.4 40.0*	39 2*	1 0*	2.6 0.0*
				R.D.E. = 1.94					
5th day and over + ?	53 8*	12 4*	22.7 50.0*	71 11*	5 3*	7.1 27.3*	50 6*	9 5*	18.0* 83.3
				R.D.E. = 2.4					

\* Bacteremia.

There are many hazards in the attempt to make accurate interpretations of chemotherapeutic experiments. Chesney,<sup>8</sup> many years ago, demonstrated that, prior to the development of an active logarithmic phase of growth, there was a definite lag in the multiplication of organisms *in vitro*. It would certainly seem that an organism subjected to the action of a chemical agent while in a lag phase of growth, *in vitro*, might be inhibited in its growth to a greater extent than when in its logarithmic phase. Under such conditions, an unwarranted degree of activity might be attributed to the influence of the drug. Nevertheless, it appears as though few investigators of sulfapyridine have observed the precaution of inoculating organisms in the active logarithmic phase of growth. In McIntosh and Whitby's<sup>27</sup> experiments, a highly virulent organism in the active logarithmic phase of growth was always used. In their experiments non-immune mice inoculated with pneumococci inevitably developed bacteremia despite sulfapyridine therapy. Immune

mice, on the other hand, inoculated with the same number of organisms, failed to develop bacteremia. These differences in behavior occurred despite the fact that both groups of mice were ultimately cured.

Our own observations have indicated that pneumococci may remain viable for as long as 54 hours, despite the presence of sulfa-

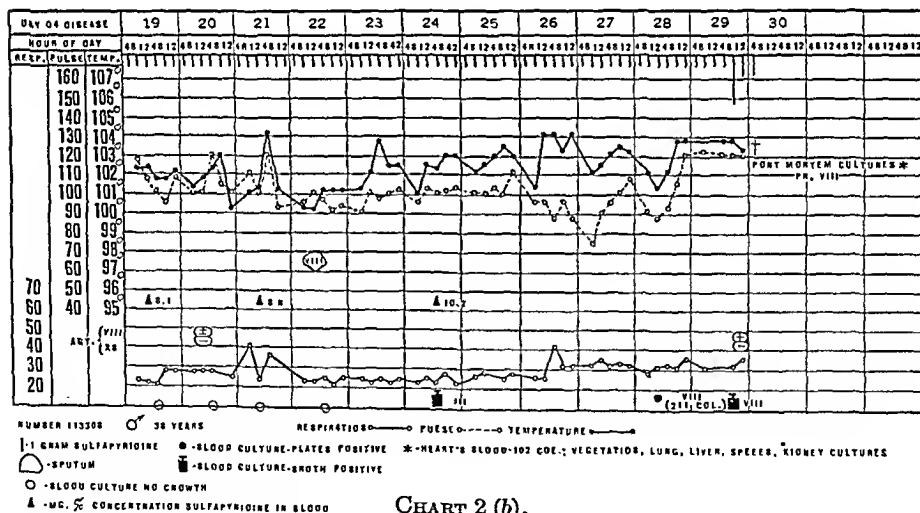
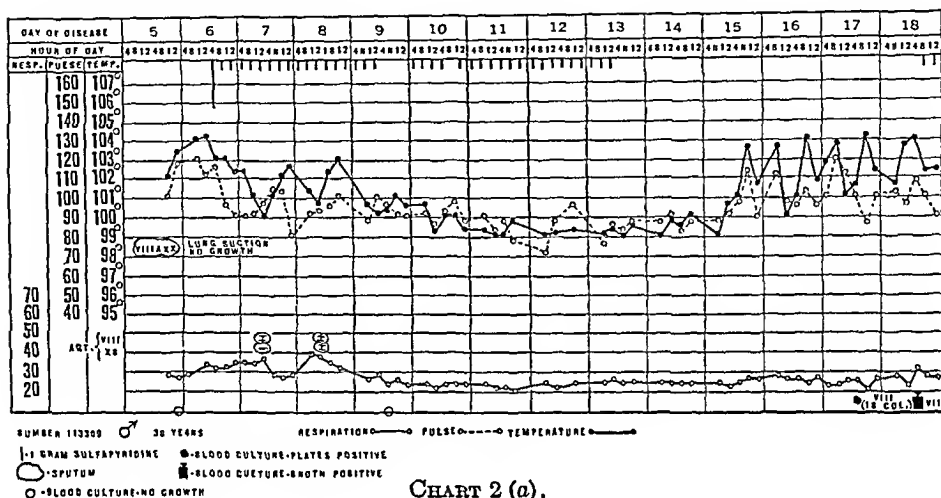


CHART 2.—(a) and (b). Fever charts of patient in whose sputum Pn. VIII and Pn. XX were found. Forty-eight hours after discontinuing sulfapyridine, the temperature rose. The blood became invaded with Pn. VIII; signs of aortic valvular disease developed. The condition was uncontrolled by subsequent administration of sulfapyridine. Agglutinins were present and the blood culture positive simultaneously. Postmortem: vegetative endocarditis.

pyridine and serum, and that large inocula may undergo temporary bacteriostasis with subsequent overgrowth. The significance of such observations to human therapy is well indicated by the following case whose fever chart is shown in Chart 2. A man of 39 was



treated with sulfapyridine on the 6th day of his illness, receiving the drug for the next 7 days. His temperature was below 100° F. on the 12th and 13th days, when the drug was stopped. On the 14th day the temperature reached 100° F.; on the 15th day the temperature reached 103.8° F., and continued until the 18th day, at which time a blood culture taken on the 17th day grew a pneumococcus VIII. Previous blood cultures had been sterile. In spite of the continuation of sulfapyridine therapy and the development of agglutinating antibodies, this patient died on the 29th day and autopsy confirmed the diagnosis of bacterial endocarditis. Whitby had earlier shown that sulfapyridine had no effect upon the quality, quantity or speed of production of specific antibodies, and felt that it would be unwise to sacrifice the methods of immune therapy which had already been proven valuable.

That there are additional difficulties in attempting to evaluate chemotherapeutic agents by animal experimentation, are indicated by the differing reports of such workers as Cooper, Gross and Lewis,<sup>10</sup> and Hilles and Schmidt.<sup>20</sup> The former workers reported little advantage of sulfapyridine over sulfanilamide in the treatment of pneumococcal infections in mice and pneumococcal meningitis in rats. However, the treatment dose employed by them was small, only 20 mg. of either drug at 3, 23, 47 and 72 hours after infection for the mice, and 20 mg. at 6, 13 and 23 hours after infection followed by 20 mg. once daily for 8 doses in the rats. By these methods of therapy, sulfapyridine proved to be of only slightly greater therapeutic action than sulfanilamide. Hilles and Schmidt, working with Type XXII infections in mice, found that with a dosage of 20 mg. orally at 2, 6, 12, 18 and 24 hours with an additional 24-hour, 20-mg. dose for 5 successive days, only 1 out of 20 mice survived for 30 days, though life was slightly prolonged in the remaining 19. Where therapy was changed to 20 mg. 2 hours after infection, then every 6 hours for 4 days, then at 12-hour intervals for 2 days, 14 of 20 mice lived for 30 days, and of the remaining 6, 4 died after discontinuance of therapy. Raiziss, Severac, Moetsch and Clemence,<sup>33</sup> using an even less adequate dosage than Cooper, Gross and Lewis, concluded also that sulfapyridine was not much more effective than sulfanilamide. Long, Bliss and Feinstone,<sup>24</sup> using a dosage intermediate between that of Cooper, Gross and Lewis, and Hilles and Schmidt, reported intermediate results in the therapy of pneumococcal infections in mice.

Some uniform standard dosage, as well as strains of uniform resistance and in the same phase of growth, should be employed in order that there may be accurate comparable results. This is of particular importance to the clinician who desires information in order to establish the most efficient form of therapy. For the present we must conclude that the optimal conditions and combinations in our therapy of the pneumococcal pneumonias have not been deter-

mined. Considerably more careful work must be done before the rôle of serum and of sulfapyridine can be formulated.

**Summary and Conclusions.** 1. In marrow cultures, the presence of sulfapyridine in concentrations of 5 mg. or more per 100 cc. may lead to ultimate sterility with inocula of 500 or less per cc. of Types I, III or VII pneumococci, whereas controls uniformly grow out to numbers of over 100 million colonies per cc.

2. The larger the initial inoculation, the less likely is sulfapyridine to lead to sterility.

3. Sulfapyridine alone is definitely more effective against pneumococci than equi-molar concentrations of sulfanilamide.

4. The presence of type specific antiserum almost always increases the effectiveness of sulfapyridine. With the same concentrations of sulfapyridine, increasing quantities of antibody are increasingly effective. Occasionally, for some undetermined reason, the presence of serum interferes with the bactericidal action of sulfapyridine *in vitro*.

5. Within the range of concentrations employed varying from 1 to 10,000 to 1 to 100,000, an increase in concentration of sulfapyridine results in an increase in effectiveness.

6. Different strains of pneumococci appear to vary in their susceptibility to the action of sulfanilamide and sulfapyridine. Freshly isolated virulent strains appear to be less susceptible than strains after they have been grown for some time in ordinary media.

7. The presence of sulfapyridine does not result in rapid death of all organisms present. Small numbers of living organisms may be present for several days in cultures which appear microscopically sterile.

8. Sulfapyridine, in the concentrations employed, has not yet appeared to damage directly the marrow cells nor to favor or inhibit phagocytosis.

9. Organisms exposed to the action of sulfapyridine undergo no loss of capsule or type specificity. They may, however, become distorted, develop long chains and stain irregularly.

10. Acetyl sulfapyridine is ineffective.

11. Serum from untreated pneumonia patients is not bactericidal. The serum from treated patients has bactericidal activity roughly proportional to sulfapyridine and serum content.

12. Sulfapyridine alone gave a lower death rate than either serum alone or serum plus sulfapyridine, in a series of 324 adult patients rotated for treatment. The lowest mortality rate was observed in cases treated early (1 to 4 days) with serum and sulfapyridine. The results in children were inconclusive and in infants did not show the trend in adults.

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## A FATAL CASE OF HEMOLYTIC ANEMIA AND NEPHROTIC UREMIA FOLLOWING SULFAPYRIDINE ADMINISTRATION.

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SULFAPYRIDINE ("Dagenan" or "M & B 693") recently released to the medical profession, has rapidly come into fore and has in many institutions almost entirely superseded serum therapy in the treatment of pneumonia. It is therefore pertinent at this stage of the problem to report all known cases wherein toxic or even fatal results were obtained with this drug. The present case is, we think, the first of an acute fatal hemolytic anemia and renal insufficiency as caused by sulfapyridine to be reported in the literature.

**Case Report.** H. L., a 79-year-old white man, was admitted to this hospital on March 17, 1939, with the chief complaint of abdominal distention and vomiting of 4 days' duration. On *physical examination* he appeared to be an acutely ill old man. Abdomen was markedly distended, but not

tender. Basal râles were heard in the left lung. (T. 100° F.; P., 100; R., 24; B. P. 164/100). *Blood examination* on admission showed a leukocyte count of 19,000 per cc. (84% neutrophils). *Blood chemistry*: glucose, 144.6 mg.; urea nitrogen, 24.4 mg.; non-protein nitrogen, 49.4 mg.; and creatinine, 2.7 mg. per 100 cc. The icteric index was 10.1 units with a direct immediate positive van den Bergh.

A diagnosis of partial low intestinal obstruction and pulmonary congestion was made on admission, and treatment was at first directed towards the relieving of the intestinal obstruction. On March 20, the 3rd day after admission, the pulmonary findings became more pronounced and a diagnosis of pneumonia was made. On March 22, sulfapyridine therapy was started. The first dose of 1 gm. was given at 10 P.M. Thereafter, for the following 2 days, the drug was given in doses of 1 gm. 4 times a day, until a total of 8 gm. was consumed by the end of the 2d day. On March 25, the patient began to show an anemia and his skin took on a yellow hue.

*Blood examination* that day showed a marked drop of hemoglobin and red blood cells. On March 23, the first day after sulfapyridine administration, the hemoglobin was 80% and the erythrocyte count 4,000,000 per cc. On March 25, the hemoglobin fell to 58% and the erythrocytes to 2,750,000 per cc. Leukocyte count was 18,500 per c.mm. with 66% neutrophils, 2% metamyelocytes, 2% myelocytes and 30% lymphocytes. The erythrocytes showed marked anisocytosis, poikilocytosis and polychromasia, and contained 4% of nucleated forms. The urine became port-wine in color, was positive for blood and bile and contained 10% of packed coagulated erythrocytes.

Sulfapyridine was immediately discontinued and a continuous intravenous administration of 5% glucose and saline was begun. The *blood* on the following day, March 26, showed an icteric index of 20.5 and on March 27, it rose to 30.5, with an immediate direct positive van den Bergh. The blood glucose was 421 mg.; urea nitrogen, 222; non-protein nitrogen, 258; and creatinine 8.86 mg. %. The sulfapyridine content of the blood was 11.5%. Leukocyte count was 26,000 per c.mm. with 65% neutrophils. The nucleated red blood cells increased to 8%. The temperature rose to 102.5° F. Pulse varied between 100 and 115 and respiration between 20 and 26 per minute. In spite of the discontinuation of the drug, the patient passed into a semi-stuporous state and his jaundice deepened. The following day, March 26, two transfusions of 250 cc. and 500 cc. of citrated blood, respectively, were given with no untoward effect. The following day, March 27, 9 days after admission, the uremic state deepened, and at 3 P.M., 65 hours after administration of sulfapyridine, he died. He had complete anuria for 36 hours preceding death.

*Autopsy* (3 hours after death) revealed the following pertinent findings: jaundice of skin, conjunctivæ and viscera; partial intestinal obstruction in the region of the ascending colon caused by a fibrous band; suppurative bronchitis, emphysema and basal atelectasis and sclerosis of coronary vessels. The *kidneys* were moderately enlarged. They weighed 175 gm. and measured about 12 by 5.5 by 3 cm. each. Capsule stripped with ease. Surface was finely granular. On section, throughout the cortex and medulla, and especially at the cortico-medullary junction, there were numerous brownish specks arranged in coalescent longitudinal streaks which made the outline of the rays prominent.

*Microscopically*, the most profound changes were found in the kidneys and the liver. The *kidneys* (Figs. 1-5) showed the majority of the tubules to be plugged with collections of golden-yellow or brownish pigment casts or hemosiderin-laden macrophages and clumps of granular "shadow" erythrocytes. This was mostly noted in Henle's loops, the recurring limbs and collecting tubules. In many tubules (Figs. 2, 3), the free and intra-

cellular pigment plugged and distended the lumen's causing pressure atrophy and thinning of their lining epithelium. In a smaller number (Fig. 3), the tubular epithelium contained coarse brownish hemosiderin granules within the cytoplasm, and the cells, including the nuclei showed varying stages of degeneration. Beginning calcium deposition around few tubular casts were noted (Fig. 4). No evidence of tubular regeneration was found. The proximal portions of the tubules were widely dilated (Fig. 5.) The glomeruli showed relatively few changes compatible with those found in the aged. The *liver* (Fig. 6) showed patchy cytoplasmic vacuolization, with a tendency towards central localization. The Kupffer cells were increased in number and loaded with hemosiderin pigment. In the *spleen*, the reticulo-endothelial elements were very prominent and contained abundant hemosiderin pigment. The *bone marrow* showed a moderate degree of hyperplasia of the erythropoietic elements. *Prussian blue* stains demonstrated the presence of iron-containing pigment in the tubular casts, the Kupffer cells, the reticulo-endothelial elements of the spleen and, to a lesser degree, in the liver cells, and occasionally in the epithelium of the renal tubules.

**Pathologic Diagnosis.** Acute hemolytic anemia with hemosiderosis of the liver, spleen and kidneys; fatty degeneration of liver; widespread obstruction of renal tubules (mainly of Henle's loops, recurring limbs and collecting tubules), with secondary dilatation of proximal tubules and a moderate degree of tubular degeneration; moderate vascular nephrosclerosis; sclerosis of coronary vessels with patchy myocardial fibrosis; partial obstruction of ascending colon, caused by bands of adhesions, as a sequela of a prostatectomy operation; chronic suppurative bronchitis, pulmonary emphysema and bilateral basal atelectasis; moderate hyperplasia of the bone marrow.

**Discussion.** As far as we could ascertain, this appears to be the first reported fatal case of acute hemolytic anemia occurring during sulfapyridine treatment. In evaluating the exact cause of death in our case, we cannot lose sight of several contributory factors which were present. The co-existing partial and moderate intestinal obstruction and the senile, "decreased" cardiovascular and renal lesions, though, *per se*, rather moderate, deserve special consideration. The intestinal obstruction was undoubtedly the cause of the moderate retention of the nitrogenous products in the blood on admission. However, after careful consideration of the gross and microscopic findings, we are prepared to relegate it to a minor place, especially since under treatment the signs of obstruction subsided considerably. On the other hand, the sudden and dramatic onset of the acute hemolytic anemia, with its resulting complete renal shut-down, as so clearly demonstrated by the tubular blockage, coupled with the severe liver damage, leave no doubt in our mind that it was sulfapyridine which was directly and mainly responsible

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#### LEGENDS FOR FIGS. 1, 2 AND 3.

FIG. 1.—Kidney showing plugging of tubules, mainly in the medulla and cortico-medullary junction and secondary dilatation of the proximal portions of the tubules in the cortex. (× 12.5.)

FIG. 2.—Kidney showing plugging of tubules in the medulla with pigment casts and secondary pressure atrophy of the tubular epithelium. (× 100.)

FIG. 3.—Kidney showing in addition to plugging of lumen of tubules with hemoglobin pigment and shadow erythrocytes also hemosiderosis of the epithelium and various stages of necrosis of the epithelium proper. (× 300.)



FIG. 1

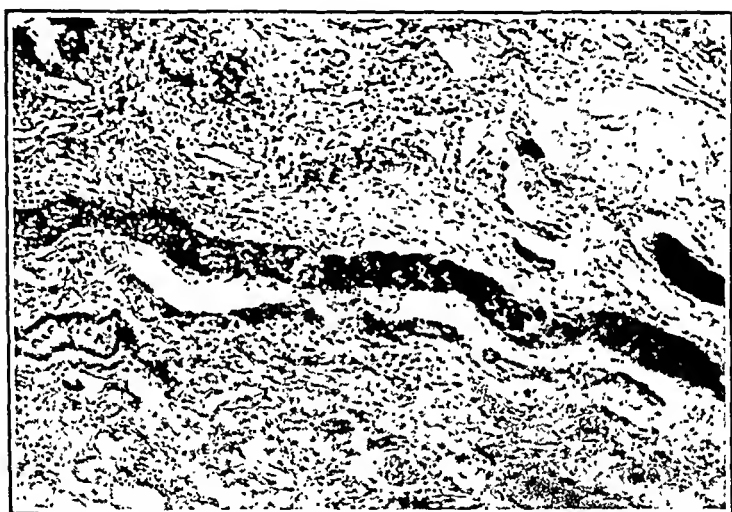


FIG. 2



FIG. 3



FIG. 4



FIG. 5



FIG. 6



FIG. 7

FIG. 4.—Calcium deposition on a pigment cast in one tubule. ( $\times 450$ .)

FIG. 5.—Secondary dilatation of the proximal convoluted tubules in the cortex and a few plugged distal segments of the tubules. ( $\times 450$ .)

FIG. 6.—The liver showing fatty degeneration with a tendency towards localization in the central part of the lobule. ( $\times 25$ .)

FIG. 7.—The kidney after death due to transfusion with incompatible blood, showing plugging of tubules with hemoglobin pigment and secondary thinning of tubular epithelium. ( $\times 450$ .)

for the death of the patient. The other factors enumerated above can, at most, be considered as contributory.

Reviewing the literature<sup>5,8,9,11-13,15,18</sup> on acute hemolytic anemia due to the closely allied drug, sulfanilamide, it is seen that, under prompt treatment, which consisted mainly of transfusion and immediate withdrawal of the drug, recovery took place in most of the patients.

There is only one recorded fatal case of acute hemolytic anemia caused by sulfanilamide (Wood<sup>21</sup>). A comparison of Wood's case with our own reveals several interesting similarities. The jaundice and anemia were noted in both cases on the third day of administration of the drug. The necropsy findings in Wood's patient are similar to ours, being mainly those of hemolytic anemia with hemosiderosis of liver, spleen and kidneys and blocking of the kidney tubules with hemoglobin casts. However, no stress is laid in Wood's report on the tubular obstruction, nor are there any blood chemistry figures available for study of the renal function.

It is interesting to note that the time interval of 3 days for the onset of the anemia in our case was about the same as that observed by Long.<sup>11</sup> He also found that this had no relation to the total amount, nor to the size of the individual doses of the drug administered.

The renal lesion and even the clinical features of our case bear a striking similarity to those seen in some of the patients who die as a result of transfusion with incompatible blood. The latter exhibit also all the features of true renal insufficiency with widespread changes in the renal tubules and hemosiderosis of the liver and the reticulo-endothelial system. They also show either a blocking of the distal segments of the tubules by pigment casts and secondary dilation of the proximal portions, or varying degrees of degenerative changes in the tubular epithelium itself.

An even more striking similarity with the anatomic findings in our case is seen in those of experimental renal insufficiency, as obtained by DeGowin and his associates.<sup>4</sup> The majority of their dogs, who died from renal insufficiency, as a result of injection with a solution of canine hemoglobin, showed pathologic lesions that are almost identical with those in our case, as well as in a number of reported deaths after transfusion and in one case after quinine administration. (Bordley;<sup>3</sup> Goldring and Graef;<sup>6</sup> Baker and Dodds;<sup>2</sup> Witts;<sup>20</sup> Shera;<sup>16</sup> Ravid\* and Terplan and Javert.<sup>19</sup>) The main lesion in all these was obstruction of the tubules by hemoglobin pigment (Fig. 7). The other lesion, namely necrosis of the tubular epithelium, which in some transfusion cases, as well as in a number of DeGowin's dogs, was more prominent, was also seen in our case, but only to a lesser degree.

\* Ravid, J. M.: A case of death following transfusion with incompatible blood, in a woman of 42 (unreported). Microphotographs of the kidney of this patient accompany text (Fig. 7).



We can, therefore, conclude from the anatomic lesion in our case, that the tubular obstruction and, to a lesser degree, the degenerative changes in the tubular epithelium, were the salient factors in the mechanism of renal insufficiency and uremia.

Recently, 3 cases of "hematuria, abdominal pain and nitrogen retention, following sulfapyridine administration" were reported by Southworth and Cooke.<sup>17</sup> In commenting on their cases, the authors state that "the mechanism underlying the development of these complications has not definitely been determined."

It seems to us, that in the light of the anatomic findings in our case, coupled with those in the case of Lawrence<sup>10</sup> in man, and in the experimental work of Oakley.<sup>14</sup> Antopol and Robinson<sup>1</sup> and Gross, Cooper and Lewis,<sup>7</sup> who saw the formation of uroliths after the administration of sulfapyridine and prontosil, the pathogenesis of the above 3 cases can also be reasonably explained. The symptomatology of these cases, not excluding the one that simulated acute appendicitis, was clearly of renal origin, as it was accompanied or immediately followed by gross hematuria. The pain was most probably due to distention of the kidney as a result of varying degrees of urinary retention or to impaction by a freshly formed calculus along the urinary tract.\* The main lesion, most likely, was a partial blockage of the renal tubules by crystals or hemoglobin pigment, as a result of hemolysis and perhaps also a certain degree of degeneration of the tubular epithelium as a direct nephrotoxic action of the drug. This in turn must have resulted, first, in hematuria and, soon after, in suppression of urine, azotemia and uremic manifestations. The initiating process of this anatomic lesion, most likely, was either hemolysis or calculous impaction. At the same time, as seen in our case, in addition to the mechanical tubular blockage, another, so-called nephrotoxic factor, may have operated in their cases as well. It is also interesting to note that the dosage in these, as in other cases, was not a deciding factor. The total amount in all 3 cases was much higher than in ours (52 gm., 25 gm. and 10 gm. in authors' cases, as against 8 gm. in our case.)

**Summary and Conclusions.** 1, A case of fatal acute hemolytic anemia and uremia during the course of treatment with sulfapyridine, is reported here. It occurred on the third day of treatment, and only after a total of 8 gm. of the drug was consumed.

2. The salient pathologic lesions, directly caused by sulfapyridine were twofold: *first*, those secondary to the resultant hemoglobinemia and hemoglobinuria, viz., obstruction of renal tubules by hemoglobin pigment and its derivatives, and hemosiderosis of liver, kidney and the reticulo-endothelial system; and, *second*, those produced

\* The fact that the Roentgen rays were "negative" does not exclude the presence of calculi because, as pointed out by Antopol and Robinson,<sup>1</sup> the uroliths consisting of the acetyl derivative of sulfapyridine permit penetration by Roentgen rays. It is only when calcium is deposited about these concretions which act as a nucleus that their shell may become Roentgen ray opaque.

as a direct action on the hepatic and renal epithelia proper. The latter lesion was minimal in this case.

3. The formation of urinary calculi must also be taken into account in the summation of the toxic effects of sulfapyridine on the urinary apparatus in general.

4. The clinico-pathologic picture, as induced by sulfapyridine, is not a syndrome *sui generis* for this drug alone, but appears to be analogous with those encountered in deaths after transfusion with incompatible blood, in blackwater fever, paroxysmal hemoglobinuria and poisoning with certain chemicals.

5. Careful daily observations of the patient, especially of the aged, with regard to the blood picture and the renal function, and the immediate discontinuance of the drug upon the detection of any deleterious effects on the kidneys and blood, should, among other things, be guiding principles in the treatment with sulfapyridine.

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#### PARENTERAL ADMINISTRATION OF SULFAPYRIDINE.

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IN the ordinary course of treatment of pneumococcic infections with sulfapyridine one frequently encounters situations which make the oral route of administration either impractical or impossible. Experience here and elsewhere has shown that nausea and vomiting may assume such troublesome, and sometimes even such serious

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proportions as to prevent effective use of the drug by mouth. Furthermore, special occasions arise in which it is difficult to effect satisfactory therapy *per os*. Among these situations may be: 1, the treatment of comatose patients; 2, the treatment of any urgent condition which requires an immediate, adequate, therapeutic blood level; and 3, the raising of the drug concentration in a localized area to a level equal to or higher than that in the blood, as, for instance, in the subarachnoid space of patients with meningitis.

A number of methods have been employed to obviate the above-mentioned difficulties. Almost every clinical investigator has mentioned some mode of administration which he believed would overcome the commonest of the ill-effects, namely, the nausea and vomiting. Early were mentioned the use of some soft food such as applesauce, of soda bicarbonate, or of milk. Later, rectal instillations of the drug were employed but without sufficient benefit to warrant their continued trial. Here we resorted to tablets coated with salol. In a few cases there was some slight alleviation of the gastric distress, but this improvement was hardly universal enough to be called satisfactory. Still later we resorted to the administration of 20 to 30 cc. of colloidal aluminum hydroxide just preceding each dose of pills. Again the adjuvant seemed to help the occasional patient but in many cases it only served to increase vomiting. Whitby<sup>7</sup> and later Hobson and McQuaide<sup>1</sup> suggested the use of an oily suspension of sulfapyridine for injection into those patients who, by virtue of their upset stomach or of their comatose condition, were unable to take the drug by mouth. Long<sup>2</sup> pointed out the objections and dangers of this method. Recently Marshall and Long<sup>5</sup> have advocated the use of the sodium salt of sulfapyridine by the intravenous route, in order to maintain a satisfactory blood concentration in the face of these obstacles.

With the exception of the sodium salt, with which we have had no experience, none of the suggested methods of altering the mode of administration to lessen the unpleasant side reactions has proven entirely satisfactory in our hands. In general, the incidence of nausea and vomiting does not seem to have been materially altered; the oft-mentioned "irregularity of absorption" does not seem to have been obviated and the patient does not seem to have been relieved of disturbing treatments. Comatose and other severely ill or unresponsive patients have still presented a definite therapeutic problem with respect to a quick attainment of an effective concentration of the drug in the blood. Furthermore, in the case of diabetics and cardiacs with pneumonia it has been almost imperative to find some method of giving the medication with a minimum of ill-effects.

**Experimental.** Early in our work with pneumonia patients we attempted to give sulfapyridine\* by hypodermoclysis. A few ex-

\* The sulfapyridine powder used was obtained through the courtesy of Merck & Co.

periments with animals served to show that, when the drug was introduced as a solution under the skin, there was no evidence of local tissue damage. We then observed that adequate blood levels could be maintained by the parenteral route alone; that the dosage required to produce a therapeutic effect was somewhat smaller than the usual oral dose. We therefore investigated the solubility of the pure powdered sulfapyridine, using several concentrations of the drug in a number of different solutions. The object throughout this work was to find a fluid suitable for parenteral administration which, at the same time, would carry more than the orthodox 1 gm. of sulfapyridine per liter. Added impetus was given this work by the successful treatment of 2 comatose cases of pneumococcus meningitis. This treatment was, of necessity, entirely by the parenteral paths for the first few days.

The results of our solubility studies on sulfapyridine are shown in Table 1.

TABLE 1.—SOLUBILITY OF SULFAPYRIDINE.

Amount of sulfapyd. added to 100 cc. of solvent, gm.	Amount of sulfapyridine found dissolved when analyzed.					
	Distilled water 20° C. = 6 hrs., gm.	Saline .085% 16° C. = 8 hrs., gm.	.85% saline 5% glucose 16° C. = 20 hrs., gm.	Saline .35% 37° C. 8 hrs., gm.	Glucose 5% 16° C. = 24 hrs., gm.	.85% saline 5% glucose 25° C. = 4 days, gm.
0.050	0.052	0.052	0.052	—	0.047	—
0.100	0.097	0.101	0.103	—	0.094	—
0.150	0.141	0.157	0.154	—	0.143	—
0.200	0.141	0.130	0.174	0.208	0.187	0.187
0.250	0.084	0.091	0.163	0.190	0.224	0.245
0.300	0.085	0.087	0.160	0.168	0.239	0.279

It will be seen from these observations that the solubility of sulfapyridine is a function of at least two different factors: 1, the type of solvent; and 2, the temperature of the solution. At first it was thought that the increased solubility in glucose might have been due to a combination of the drug with the sugar but determinations of the glucose content of the solutions before and after the addition of the drug failed to show any significant variation in glucose concentration. Furthermore, since the amounts of sulfapyridine recovered from the solutions analyzed approximated so closely those which had been introduced, it seemed evident that if any combination had been effected between the glucose and the sulfapyridine, it must have been so loose as to be unimportant.

For the administration of sulfapyridine parenterally it is clear from these solubility studies that a 0.15% solution in 0.85% saline or a 0.2% solution in 5% glucose solution or in equal parts of normal saline and 5% glucose solution is practical, and such has proved to be the case, provided the solutions are not allowed to cool below room temperature.

**Methods.** The method used in preparing these solutions for analyses was identical with that which we have been using in the preparation of the sulfapyridine for therapeutic purposes. A weighed amount of the powdered drug was poured into the desired volume of the liquid to be tested or used. This liquid had been brought to the boiling point just before the addition of the powder. The mixture was shaken vigorously until all the powder had gone into solution, usually for 1 or 2 minutes. (Occasionally it seemed expedient to heat the mixture again to the boiling point in order to facilitate complete solubility.) The solution was then allowed to cool for 6 to 8 hours or until it had reached room temperature. Portions of these mixtures were then analyzed for their sulfapyridine content. (Therapeutically the solutions were generally cooled fairly rapidly to the desired temperature.)

The determinations were made with a modification of the sulfanilamide method described by Marshall and Litchfield.<sup>4</sup>

1. To 20 cc. of a 1 to 20 dilution of oxalated blood in water are added 5 cc. of 15% trichloroacetic acid.

2. To 1 cc. of a 1 to 8 dilution of the standard aqueous 10 mg. % solution of sulfapyridine are added 2 cc. 15% trichloroacetic acid and 7 cc. distilled water. (This ultimate dilution contains 0.0125 mg. sulfapyridine and is suitable for use with blood levels of 1.5 to 4.5 mg. %. Other dilutions may be made by varying the volume of 1 to 8 dilute standard, adding the acid and then making the volume up to 10 cc.)

3. To 10 cc. of blood filtrate or acidified standard are added 1 cc. of fresh 0.1% sodium nitrite.

4. After 3 minutes add 1 cc. of the molar sodium acid phosphate buffer containing ammonium sulfamate.<sup>4</sup>

5. After 2 more minutes add 5 cc. of alcoholic dimethyl alpha naphthylamine (1 cc. of dimethyl naphthylamine in 250 cc. 95% ethyl alcohol).

6. Wait 10 minutes and then compare in a colorimeter.

The error in this method was determined to be between 2 and 4% when calibrated instruments were used and the fluids analyzed were diluted to contain no more than 15 mg. % of sulfapyridine.

The solutions were observed to assume a pale golden color upon standing. Whenever the sulfapyridine precipitated out, it seemed to carry more and more of the substance with it so that after a day or two a considerable clump of powder could be visualized on the bottom of the flasks. However, when solution was complete, the sulfapyridine remained dissolved for several days. Aërobic and anaërobic cultures of such fluids were found to be sterile.

**Clinical Application.** In the present series there are 43 cases which have received sulfapyridine parenterally, as shown in Table 2. In Table 3 are given the 16 cases which received sulfapyridine by the parenteral route exclusively except in 2 cases which received some oral treatment.

TABLE 2.—CASES TREATED WITH PARENTERAL SULFAPYRIDINE.

Intravenous alone . . . . .	2
Intravenous plus subcutaneous . . . . .	4
Subcutaneous alone . . . . .	10
Subcutaneous supplementary to oral . . . . .	27
Total . . . . .	43

We have had no difficulty in maintaining adequate blood levels by this method even over periods of a week or more (Cases 99 and 97). Furthermore, we have had an opportunity to study the

favorable therapeutic response which may be attained by this method of administration (Cases 103, 109, 96; Charts 1-A and 1-B). In addition to the subcutaneous and intravenous routes, we have introduced the solution routinely into the subarachnoid space in our cases of meningitis, and in 2 cases of empyema we have replaced the empyema fluid by a slightly smaller quantity of sulfapyridine solution.

The fundamental plan of therapy has been to administer the drug to the extent of 6 gm. in the first 24 hours and then to maintain the blood concentration by means of 4 gm. daily thereafter. For this purpose in almost every case the sulfapyridine was made up in 2-gm. lots. Each 2-gm. portion of the drug was contained in 1500 cc. of normal saline, in 1 liter of 5% glucose, or 1 liter of aliquot portions of normal saline and 5% glucose. The desired

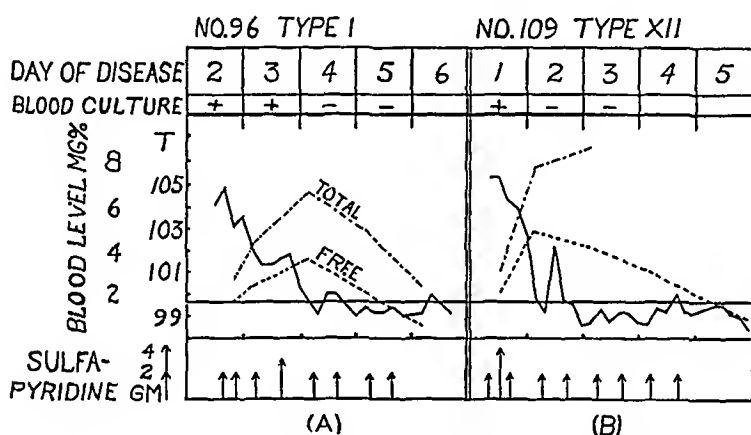


CHART 1.—Patients treated exclusively with parenteral sulfapyridine.

daily total could then be administered in as many individual treatments as seemed indicated. However, with each patient we tried to space the injections equally throughout the 24 hours; that is, every 8 hours (for 3 injections) or every 12 hours (for 2 treatments).

As can be readily seen in Chart 2-A, after an initial dose of 2 gm. the peak level of sulfapyridine in the circulation is attained at different times, depending on the route employed. The intravenous route gives its highest readings immediately after the solution has been introduced. On the other hand, hypodermoclysis affords its optimum level from 2 to 4 hours after the treatment has been completed. These levels compare more than favorably with the levels obtained by Schmidt and Hughes<sup>6</sup> and by Long<sup>3</sup> after an oral dose of 2 gm. or more of sulfapyridine.

It occurred to us that if the above observations were valid, it would be decidedly more efficacious to inaugurate the therapy in critical cases by a combination of these two approaches. Accordingly, 2 cases were treated as follows: After the type of pneumo-

coccus had been determined and the method of administration had been decided, a clysis of 2 gm. of sulfapyridine in 500 cc. of normal saline and 500 cc. of 5% glucose was started. While this solution was being absorbed, 2 gm. of sulfapyridine in 1000 cc. of 5% glucose were given intravenously. Chart 2-A shows that the sulfapyridine concentration in the blood is maintained at an almost constant level with the combined therapy. *A priori*, this procedure would certainly seem preferable to the others outlined.

However, in all fairness, it must be stated that, if it is desired to use one method exclusively, satisfactory blood levels may be maintained by giving the initial treatments oftener than every 12 hours. In this way accumulation of the drug occurs. Chart 2-B shows

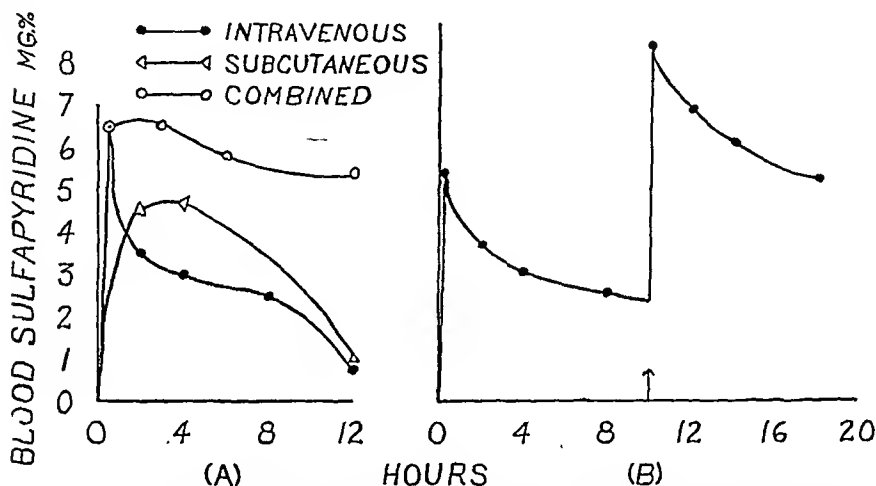


CHART 2.—Blood levels of patients treated with parenteral sulfapyridine. Initial dose, 2 gm.; 2 gm. by each route in combined treatment. (↑ indicates second dose of 2 gm. of sulfapyridine.)

such a procedure carried out by the intravenous route. In this case (No. 103) the second infusion of sulfapyridine was given about 10 hours after the first. Whereas, the figures for the 2-, 4- and 8-hour levels correspond very closely with those given for the single intravenous dose in Chart 2-A, the levels in the second 8-hour period were very much higher. Thereafter the blood concentration was readily maintained by injections every 12 hours (Table 3).

To date we have had only one local reaction following sulfapyridine given in the above described manner. One patient developed thrombophlebitis of the superficial thigh veins adjacent to the site of the injection. It seems likely that there was an error in technique to account for this accident, for nothing of a similar nature appeared in the opposite leg where concomitantly some of the same solution was being run in from the other arm of the "Y" tube of the same clysis set. Furthermore, we have observed no immediate

TABLE 3.—CASES TREATED WITH PARENTERAL SULFAPYRIDINE EXCLUSIVELY.\*

Case No.	Day of disease treatment started.	Route.	Dosage.	Blood levels†—days.					
				1st. (4 hr.)	2d.	3d.	4th.	5th.	6th.
103 (G. W.)	9th	I-v.	2 gm. 3 times in 1st 24 hrs.	3.1, 3.4	5.3, 6.0	5.4, 7.4	6.6, 8.0	10.8, —	6.0, —
107 (J. M.)	3d	I-v.	2 gm. q. 12 hrs. thereafter	3.0, —	2.8, 3.8	5.7, 7.4	—	6.1, —	—
146 (T. S.)	9th	I-v. + sci. oral	2 gm. q. 12 hrs. thereafter	6.2, 6.6‡	4.9, 6.3	7.0, 8.9	—	—	—
159 (H. D.)	1st	I-v. + sci.	2 gm. i-v. and 2 gm. sci. simul. 8 hrs. later 2 gm. sci.	6.9, 8.2‡	7.4, 9.8	6.5, —	5.5, —	trace, 5.5§	3.1, 8.1
109 (F. L.)	1st	I-v. + sci.	2 gm. i-v. and 2 gm. sci. simul. 8 hrs. later 2 gm. sci.	2.1, 3.1	4.9, 7.8	4.1, 8.6	3.1, —	—	—
41 (J. L.)	2d	Sci.	2 gm. q. 12 hrs. thereafter	3.3, —	—	6.0, —	8.5, —	8.0, —	—
65 (J. DeL.)	2d	Sci.	2 gm. 3 times in 1st 24–48 hrs.	2.9, —	6.8, —	10.8, —	8.9, —	7.7, —	2.7, —
96 (L. S.)	2d	Sci.	2 gm. q. 12 hrs. thereafter	1.6, 2.5	2.3, 4.2	3.5, 6.5	2.0, 4.8	0.6, 2.3	—
101 (J. McL.)	2d	Sci.	2 gm. 3 times in 1st 24–48 hrs.	3.0, 5.2	4.9, 8.0	9.4, 11.1	9.3, —	11.2, 12.6	10.2, —
15 (M. R.)	1st	Sci.	2 gm. q. 12 hrs. thereafter	3.1, —	7.1, —	6.0, —	3.9, —	—	4.6, —
99 (B. G.)	1st	Sci.	1 gm. q. 12 h. thereafter	—	5.1, 5.5	11.2, 13.3	8.9, 15.4	6.8, 8.9	4.2, 5.9
78 (W. B.)	2d	Sci. (+ serum)	2 gm. q. 12 h. thereafter	—	—	7.8, —	4.3, —	3.9, —	—
10 (M. S.)	2d	Sci. (+ serum)	2 gm. q. 12 h. thereafter	4.6, —	6.6, —	5.8, —	5.6, —	5.1, —	—
71 (G. P.)	?	Sci.	1–2 gm. q.d. thereafter	—	1.0, —	2.3, —	4.4, —	—	—
97 (M. D.)	—	Sci. + I-v.	6 gm. orally on 1st day	—	6.3, 9.4	11.9, 16.0	12.6, 16.2	7.9, 12.3	7.4, 13.2
36 (T. G.)	?	Sci.	2 gm. parent. q. 12 h. thereafter 2 gm. twice	—	3.1, —	—	—	—	—

\* Except in 2 cases which received some oral treatment.

† The first figure in each column represents free, the second figure total sulfapyridine.

‡ Patient received only 1 gm. sulfapyridine on preceding day.

§ 3-hour levels.



reactions such as chills or vascular collapse. Thus far no serious drug reactions have occurred in any of the cases that have been treated by the parenteral methods alone. At the moment it is not clear whether this is merely a fortuitous circumstance dependent on the small number of cases comprising this particular group. In general, it is fair to say that nausea and vomiting have been somewhat less severe, but by no means eliminated when the drug is administered parenterally. However, it ought to be stated that, in the few analyses which have been performed on the vomitus of patients who have received only parenteral sulfapyridine, the concentration of the drug in the vomitus has been appreciably higher than the level which was simultaneously observed in the blood. This fact would appear to leave somewhat in doubt the controversy as to whether the vomiting and nausea are of purely central or partially local origin.

**Case Reports.** CASE 99.—B. G., aged 41, female, white, admitted in state of acute alcoholism, March 19, 1939. Onset of pain in left lower chest with cough and fever 1 day before admission. Generalized convulsions on day of admission followed by a shaking chill. In addition to acute alcoholic delirium and gastritis, examination showed physical signs and Roentgen ray evidence of left lower lobe pneumonia. Type III pneumococcus was obtained from sputum. Sulfapyridine was given by clysis and temperature fell by crisis to normal after 32 hours of therapy. Forty-eight hours later temperature rose sharply to 104° F. and then fell gradually to normal over a space of 60 hours. Blood levels are tabulated in Table 3. Patient recovered. Sulfapyridine was stopped after 9 days.

CASE 97.—McL. D., aged 40, male, white; diagnosis of subacute bacterial endocarditis due to streptococcus was established March 17, 1939. Oral therapy with sulfapyridine produced intractable nausea and vomiting so the drug was administered by clysis and infusion. Temperature fell promptly to normal and remained flat for 6 days. Finally patient began to have gradually increasing amounts of fever so drug was stopped after 10 days and blood cultures became positive again.

CASE 109.—F. L., aged 39, male, white; late in evening of March 23, 1939, patient had sudden pain in left chest followed by cough, pink sputum and a mild chill. On admission 10 hours later, patient appeared prostrated and critically ill. Type XII pneumococcus was obtained from sputum and blood culture. Patient was put in an oxygen tent and the first dose of sulfapyridine was given intravenously. Subsequent doses were by clysis. Temperature fell by crisis in 24 hours. Blood cultures taken after therapy was started were sterile and patient made an uneventful recovery. Sulfapyridine was given for 4 days (Chart 1-B).

CASE 96.—L. S., aged 40, male, white; on March 16, 1939, patient had severe chills, fever and pain in right lower chest. He was admitted the next day at which time, in addition to moderately severe diabetes mellitus, signs of right middle lobe consolidation were discovered. Type I pneumococcus was isolated from sputum. Sulfapyridine was administered entirely by clysis. Blood culture was positive on admission and remained positive for 1 day after inauguration of drug therapy but temperature fell to normal in 32 hours and patient improved markedly. Clyses of sulfapyridine were given for 5 days and diabetes was readily controlled by insulin and diet (Chart 1-A).

CASE 103.—G. W., aged 59, male, white; on March 20, the seventh day after the diagnosis of pneumonia had been made, blood culture became

positive for Type V pneumococcus, about 150 col/cc. Up to this time several attempts to type a pneumococcus from the sputum had yielded only a very heavy growth of hemolytic *Staphylococcus aureus*. Patient appeared almost moribund and W.B.C. had dropped from 15,000 to 4800 in 3 days. Intravenous therapy was instituted for 6 days. Blood cultures became negative. W.B.C. rose and patient began to improve after about 48 hours. Patient later developed a lung abscess from which hemolytic *Staphylococcus aureus* and a few Type V pneumococci were obtained. Recovery has been slow.

**Summary.** We have presented a method of administering sulfapyridine parenterally which we deem quite satisfactory. One disadvantage of the method might appear to be the relatively large volume of fluid which must be used in order to put the desired quantity of sulfapyridine into solution. On the other hand, we have demonstrated by actual trial that such volumes may be given safely to almost any case when necessary. The method will maintain adequate therapeutic blood levels. It will provide adequate fluids, salt and glucose at a time when they are often needed either because of persisting vomiting or inadequate intake in delirious or comatose patients. It can be given without fear of slough or other reactions such as may follow the use of the extremely alkaline sodium sulfapyridine. Furthermore, it may be given into any part of the body where needed, such as the veins, the subcutaneous tissue, the pleural cavities or the subarachnoid space.

We are indebted to Miss Barbara Gallup for assistance in determining blood concentrations of sulfapyridine.

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## OBSERVATIONS ON THE PHARMACOLOGY AND TOXICOLOGY OF SULFATHIAZOLE IN MAN.

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SULFATHIAZOLE,† 2-(p-aminobenzenesulfonamido) thiazole, synthesized by Fosbinder and Walter<sup>4</sup> and Lott and Bergeim,<sup>7</sup> is the thiazole analogue of sulfapyridine. The report of Van Dyke, Greep,

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† We are indebted to Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, N. J., for the sulfathiazole used in these studies.

Rake, and McKee<sup>15</sup> showed that sulfathiazole is more rapidly metabolized by mice, rats, and monkeys, and undergoes less conjugation in rats and monkeys than sulfapyridine. These workers found that the drug administered with the food of mice was no more toxic than sulfapyridine when the dose was kept at therapeutic levels. Furthermore, sulfapyridine given to rats and monkeys for 14 to 57 days was found to be more toxic than sulfathiazole. When the sodium salts of the two drugs were used, sulfathiazole appeared to have about 65% of the toxicity of sulfapyridine for LD50. The principal toxic effect was the occurrence of albuminuria and hematuria in some animals.

The therapeutic effectiveness of sulfathiazole against experimental infection has been investigated by McKee, Rake, Greep, and Van Dyke.<sup>8</sup> If sulfathiazole or sulfapyridine sufficient to make 1% of the diet was fed to mice infected with pneumococcus (9 types), meningococcus, hemolytic streptococcus, or the agent of lymphogranuloma venereum, the therapeutic effect of sulfathiazole was equal to that of sulfapyridine. Further studies by this group as well as by Barlow and Homburger<sup>2</sup> suggested that sulfathiazole was more effective than was sulfapyridine against staphylococci.

The present report offers certain observations dealing with the pharmacology and toxicology of sulfathiazole in humans. Two groups of experiments were conducted, those in which a single dose of the drug was administered orally, intravenously, or rectally, and those in which multiple doses were administered over a period of days.

**Methods and Material.** Sulfathiazole was determined by the method of Marshall and Litchfield,<sup>9</sup> hemoglobin by the method of Sanford, Sheard, and Osterberg,<sup>11</sup> and urea in blood and urine by the method of Karr.<sup>5</sup> Urea clearance was calculated on the basis of 24-hour collections of urine. Preliminary trials demonstrated that sulfathiazole added to blood could be determined satisfactorily by the Marshall and Litchfield method. Slight losses, not exceeding 5%, occurred during the determination of total sulfathiazole.

The effects of the administration of single doses were studied in a group of 9 patients. Five (Cases 5 to 9) were convalescing from pneumonia but had been afebrile at least 7 days and had received no sulfonamide medication for at least 5 days. Two (Cases 1 and 2) were suffering from skin lesions of a moderate character (varicose ulcer and neurodermatitis) and 2 (Cases 3 and 4) were awaiting discharge from the hospital following uncomplicated herniorrhaphy.

The effects of continued administration of the drug was studied in 14 patients suffering from pneumonia; 83 patients undergoing treatment with sulfathiazole have been observed for possible toxic manifestations.

**Results.** 1. *Oral Administration.* Each of 6 subjects was given a single oral dose of 3 gm. of sulfathiazole shortly before a breakfast consisting of cereal, bread, milk, and canned fruit. It is evident from Table 1 that absorption from the gastro-intestinal tract was rapid. Within 1 hour, the concentration of free sulfathiazole in the

TABLE 1.—THE FATE OF SULFATHIAZOLE ADMINISTERED BY VARIOUS ROUTES.

Patient.	Date.	Drug. gm.	Hours after admin.	Blood.		Urine.					Vol- ume, cc.
				Hb, gm. per 100 cc.	Sulfathiazole.				Ex- creted, gm.		
					Free.	Total.	Free.	Total.			
										Mg. per 100 cc.	
1. A. M. . . .	1939 Dec. 19	3 (oral)	0 1 2 4 6 8 24	0 9.3 8.5 7.3 8.5 9.3 9.6	1.5 1.5 2.3 3.5 4.6 1.2	2.0 2.0 3.6 3.5 4.7 1.2					
						68	96	.188		196	
2. B. R. . . .	20 19	.. 3 (oral)	0 1 2 4 6 8 24	0 12.0 12.4 11.5 12.0 12.0 12.0	1.2 1.2 4.8 4.5 3.4 3.2 1.2	1.2 5.3 4.8 4.0 4.0 3.3 1.3					
						125	150	.525		350	
	20	..	24	12.0	3.2	3.3	175	200	.060	30	
							63	85	1.270	1490	
3. C. C. . . .	1940 Jan. 4	3 (oral)	0 1 2.5 4 6 8 24	0 14.8 14.8 14.0 14.0 13.6 14.0	5.0 5.0 5.0 4.0 2.6 2.0 1.2	5.2 5.6 4.7 3.8 3.8 3.2 1.5					
						180	192	.332		172	Crystals
4. S. W. . . .	5 4	.. 3 (oral)	0 1 2.5 4 6 8 24	0 14.8 14.8 14.8 14.4 14.4 14.4	5.0 6.3 5.7 3.6 1.0 1.4	5.0 8.5 5.9 4.9 2.4 1.5					
						62	62	.068		108	
	5	..	24	14.4	2.4	562	637	1.340		210	
5. A. W. . . .	23	3 (oral)	0 1 2 4 6 8 24	0 13.2 13.2 13.2 .. 13.2 13.2	4.5 5.0 5.5 4.7 4.2 2.0 0.0	5.0 6.5 6.0 5.7 5.7 2.7 0.0					
						135	162	.814		500	
	24	..	24	13.2	2.0	185	282	.764		270	
6. G. B. . . .	23	3 (oral)	0 1 2 4 6 8 24	0 14.4 14.4 14.4 14.4 14.4 14.4	0.0 2.3 5.0 4.4 2.5 2.1 0.0	0.0 3.0 6.4 6.4 4.4 3.2 2.0					
						25	32	.228		70	
	24	..	24	14.4	0.0	182	270	1.180		435	
7. C. P. . . .	10	Before; 3.4 intra- ven. as sodium salt	.. 0 0.25 0.5 1 2 4 8 24	.. 13.6 13.2 12.7 12.7 12.4 11.1 12.4 12.7 11.1	0.0 0.0 8.8 7.3 5.5 4.3 3.3 2.0 0.0 0.0	0.0 0.0 9.8 8.0 6.5 5.0 4.0 2.0 2.0 0.0					
						67	142	1.330		930	
						475	562	1.460		260	
						112	142	.968		680	
8. A. L. . . .	11 10	.. Before; 3.4 intra- ven. as sodium salt	.. 0 0.25 0.5 1 2 4 8 24	.. 11.1 11.1 10.4 10.4 10.4 10.4 12.7 11.1	0.0 15.0 13.5 10.6 8.1 6.3 3.3 0.7 0.0	0.0 17.0 14.2 11.3 9.2 7.2 4.4 1.2 0.0					
						465	500	.830		166	
						317	427	.720		168	
						167	240	1.560		650	
9. R. U. . . .	11 30	.. 3 rectal as sodium salt	0 1 2 4 6 8 24	0 15.6 15.6 15.6 15.2 15.2 15.2	0.7 1.0 1.0 0.6 0.6 0.4 0.0	1.0 1.3 1.4 1.0 1.0 0.7 0.0					
						35	42	.128		300	
						25	35	.088		250	
	31	..	24	15.2	0.0	15	25	.161		645	

blood reached or exceeded 4.5 mg. per 100 cc. in 3 of 6 subjects. In 5, the blood level continued to rise and reached a maximum value at the end of the 2-hour period. Concentrations remained above 4 mg. per 100 cc. for 4 to 6 hours. One patient (Case 1), aged 58, malnourished, and suffering from a varicose ulcer of the leg, differed from the remainder of the group. A delayed rise to a maximum at 8 hours suggested impaired ability to absorb the drug. However, the maximal concentration at this time was almost the same as in the more nearly normal subjects.

In this group of 6 the highest concentration of conjugated sulfathiazole in blood was 2.2 mg. per 100 cc. with a total sulfathiazole of 8.5 mg. per 100 cc. (Case 5). A few samples of blood and urine, especially those taken soon after the drug was given, contained none of the conjugated form.

Excretion in urine accounted for 84 to 93% of the ingested sulfathiazole within 24 hours in 4 subjects in the group (Table 1). Two others excreted about 60% in 24 hours. One of the latter was the patient (Case 1) showing delayed absorption of the drug. Crystals containing sulfathiazole and of acetylsulfathiazole precipitated from the urine of Case 3. Other patients have failed to show crystals in the urine, although higher concentrations of both forms often have been observed.

2. *Intravenous Administration.* Intravenous injection of sodium sulfathiazole into 2 patients (convalescent from pneumonia) gave recoveries of 96 and 97% of the drug in the urine in 24 hours (Table 1). This yield is within the experimental error of the method employed for sulfathiazole determination, so that only traces, if any, of the drug failed to be excreted in the urine.

Changes in concentration of hemoglobin were significant in only one subject after sulfathiazole was given by the oral route and in one following intravenous administration of sodium sulfathiazole. Presumably such changes reflect alterations in blood hydration, although confirmatory evidence is lacking.

3. *Rectal Administration.* Absorption of sodium sulfathiazole administered by rectum was slow and far from complete. Only slightly more than 10% of a 3 gm. dose was found in the urine within 24 hours (Table 1).

4. *Effect of Continued Administration.* In Table 2 are shown representative blood and urine studies of patients suffering from pneumonia who were receiving treatment with sulfathiazole. One or more specimens of blood and 24-hour collections of urine, when obtainable, were analyzed daily for 1 to 12 days. Following an initial administration of 3 gm., 1 gm. of sulfathiazole was given at 4-hour intervals. (Certain patients received a second 3 gm. dose 4 hours after the first.) Blood specimens were collected at various intervals. In 60 patients, including those in Table 2, concentrations of free sulfathiazole in blood during treatment varied from 1.2 to 19 mg.

TABLE 2.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFATHIAZOLE.

Patient.	Date.	Drug, gm.	Blood.						Urine.				
			Time of day.	Hb, gm. per 100 cc.	Urea N.	Sufathiazole.				Vol- ume, cc.	Sp. gr.	Urea clear- ance, % of normal.	
						Free.	Total.	Free.	Total.				
													Mg. per 100 cc.
10. J. B.	1939 Dec. 12	6	11.00 A.M. 4.30 P.M.	12.0 12.0	7 ..	6.4 3.0	7.5 3.4	162	175	1285	1.021	102	
11. W. M.	11	4	7.30	15.6	..	2.2	3.9						
	12	6	11.00 A.M. 12.30 P.M. 4.30	13.6 15.2 12.0	7 .. ..	6.0 3.1 3.4	7.2 4.0 3.8	145	160	2775	1.018	97	
		6	11.00 A.M. 5.00 P.M.	15.2 12.4	.. 8	5.5 3.2	5.7 4.5			1220	1.014	54	
		6	11.30 A.M.	15.2	6	3.1	4.9	225	267	1810	1.013	125	
	12. M. B.	15	6	11.00	12.7	..	4.0	4.2	107	145	1725	1.016	
16		0	....	..	..	..	..	38	40	1680	1.015		
11		6											
12		6	11.00 12.30 P.M.	12.0 14.4	.. 8	11.4 8.5	14.3 12.7			1000	1.018	130	
13		6	....	..	..	..	..	435	575	330*	1.020		
13. F. H.	14	6	....	..	..	..	..	625	875	150*	1.023		
	15	6	1.00	12.0	..	3.0	4.0						
	14	2	....	..	..	..	..	325	425	525	1.024		
	15	6	1.00	13.2	7	4.9	5.7	240	350	1060	1.014	48	
	16	6	....	13.2	6	3.7	4.6	220	300	1440	1.012	124	
14. J. C.	17	6	....	..	..	..	..	165	248	1695	1.011		
	18	6	....	..	..	..	..	185	215	1115	1.012		
	19	6	....	12.7	..	3.5	4.4						
	Nov. 21	6	10.15 A.M. 12.00 P.M.	.. ..	.. ..	4.0 3.0							
	22	7	....	..	15	3.0	3.6	156	223	800	1.023	128	
15. M. J.	29	5	9.30 A.M. 11.00	.. ..	.. ..	3.7 5.1	4.1 6.5						
16. W. W.	30	6											
	Dec. 1	6	12.00 P.M.	7.7	8	4.0	5.5	257	305	1610	1.011	51	
	2	6	10.00 A.M.	6.9	7	4.5	5.2	162	212	2030	1.012	42	
	Nov. 30	6	11.30 A.M.	..	..	3.6	3.6	240	265	1670	1.023	50	
	Dec. 1	6	....	..	..	3.4	3.7	350	410	1575	1.022		
	2	6	10.00	..	..	3.4	4.7	190	212	1850	1.012		
	3	6	....	..	..	..	..	190	212	4100	1.011	68	
	4	6	....	18.4	10								
	5	0	....	14.0	..	0.5	0.8						
	6	6											
17. T. Q.	7	6	....	14.8	9	2.0	3.6	310	365	1735	1.015	159	
	8	6	....	..	..	..	..	265	352	1065	1.020		
	9-10	12											
	11	0	....	15.6	..	2.6	3.5						
	5	4	3.00 P.M.	10.8	11	5.5	6.0						
	6	6	7.00	..	..	4.8	5.5						
			2.30	12.0	8	5.2	5.4	415	737	450	1.021	101	
			5.30	..	..	4.6	4.7						
	7	6	11.00 A.M. 4.30 P.M.	11.1 ..	8 ..	4.2 4.1	4.8 4.3	306	360	*	1.013		
	8	4	11.30 A.M.	10.4	..	4.5	5.8						
18. F. M.	9	6	11.30	10.0	8	4.4	5.6	257	357	2475	1.010	39	
	10	0	10.30	10.4	7	1.0	1.4	60	79	3360	1.009	34	
	19	2											
	20	6	11.00 A.M.	12.7	20	4.2	4.2						
	21	6	12.00 P.M.	11.1	20	3.6	4.5	405	540	1300	1.019	75	
	22	6	4.00	12.7	12	4.0	4.2	323	415	1200	1.020	33	
	23	6	1.30	12.7	8	3.6	4.1	213	243	1490	1.016	44	
	24	6	2.00	..	..	3.1	3.4	270	317	1490	1.017	60	
	25	0	....	12.7	..	0.2	0.7						

TABLE 2.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFATHIAZOLE  
—Continued.

Patient.	Date.	Drug, gm.	Blood.				Urine.					
			Time of day.	Hb, gm. per 100 cc.	Urea N.	Sulfathiazole.				Vol- ume, cc.	Sp. gr.	Urea clear- ance, % of normal.
						Free.	Total.	Free.	Total.			
19. E. H.	1939											
	17	5	....	13.6	..	4.8	5.5					
	18	6	11.00 A.M.	13.2	7	3.1	4.1	300	375	1330	1.022	
	19	6	10.30	17.2	6	4.2	5.0	165	200	1375	1.012	22
	20	6	11.00	14.0	20	4.6	5.4	137	192	2700	1.011	197
	21	0	12.00 P.M.	15.2	20	0.3	1.0	135	187	3360	1.010	211
	22	0	....	..	..	..	..	55	78	2495	1.010	68
20. J. D.	Dec. 17	1										
	18	6	11.00 A.M.	12.7	..	3.6	4.1			*	1.024	
	19	6	10.30	13.2	..	3.3	4.0	200	235			
	20	6	....	..	..	..	..	410	555	670	1.024	
	21	6	....	..	..	..	..	332	485	1630	1.023	
	22	6	4.00 P.M.	15.2	12	2.7	4.0	200	260	1640	1.023	44
	23	6	1.30	15.2	11	2.5	3.2	205	247	1180	1.026	68
	24	6	2.00	13.6	11	2.5	2.8	307	350	1380	1.029	152
	25	0	....	16.0	..	1.0	1.2					
	1940											
21. E. R.	Jan. 11	8	11.00 P.M.	..	..	4.5	6.5	312	500	635	1.025	
	12	6	....	12.7	16	4.0	5.7	367	575	760	1.023	85
	13	6	1.00	12.4	12	4.6	6.6	392	625	830	1.025	60
	14	5	....	..	..	..	..	220	365	590	1.023	
	15	0	5.00	13.6	15	0.0	0.0					
22. T. B.	14	7	....	..	..	..	..	287	450	630*	1.029	
	15	6	....	12.4	21	8.0	10.4	357	485	160	1.023	38
			5.00 P.M.	..	15	3.1	6.2					
	16	6	....	..	..	..	..	412	637	420	1.026	71
	17	6	3.20 P.M.	12.0	8	3.6	5.5	285	375	430	1.026	73
23. A. H.	18	0	5.00	11.5	10	0.0	0.4					
	16	9	....	..	..	..	..	200	362	200*	1.019	
	17	6	3.30 P.M.	10.4	18	8.0	13.8	192	257	305	1.020	29
	18	6	5.00	11.1	18	5.4	8.2	275	275	570	1.022	42
	19	6	4.00	12.7	15	2.8	5.0					
	20	6	8.30	11.1	11	2.7	3.4					

\* Not a 24-hour specimen.

per 100 cc., averaging 5.45 mg. per 100 cc.  $\pm$  3.42 (standard deviation). Conjugated sulfathiazole ranged from 0 to 9.7 mg. per 100 cc. with an average concentration of 1.73 mg. per 100 cc.  $\pm$  1.87 (standard deviation). Concentrations exceeding 4 mg. per 100 cc. of conjugated sulfathiazole were observed in only 5 patients, and in each case high values for this fraction were associated with severe illness. This correlation is of interest in connection with the suggestion of Wilson, Kaely, and Cullen<sup>16</sup> that a sudden rise in conjugated sulfapyridine may serve as a warning of danger. Brown, Thornton, and Wilson<sup>3</sup> also have commented on the serious implications of elevated levels of conjugated sulfapyridine.

Although Van Dyke and his associates found that sulfathiazole was not conjugated to the same extent as sulfapyridine by animals, we are not certain that this is true in man. Comparison with the

results of Long and Feinstone<sup>6</sup> and of Stokinger<sup>13</sup> for sulfapyridine failed to show much difference in response to single doses given by the oral or intravenous routes. There was, perhaps, with continued administration of sulfathiazole less of the tendency toward the accumulation of conjugated at the expense of the free compound that often accompanies medication with sulfapyridine. Because of the great importance of the condition of the patient in determining the extent of conjugation, comparisons must be made simultaneously under identical conditions. Further studies along these lines are in progress.

Absorption of the drug proceeded nearly as rapidly in patients ill from pneumonia as in the convalescent patients listed in Table 1, although exceptions were encountered. However, only 60 to 80% of the administered drug was recovered in the urine of these patients, somewhat less than in most controls.

5. *Effect on Kidney.* Inspection of Table 2 indicates that kidney function was temporarily impaired to a varying degree in nearly all of the patients. Oliguria was observed in 3 of 14, and hyposthenuria in 6 of 14 of the patients. Urea clearance was diminished in 9 of 14 patients during sulfathiazole therapy to 50% or less of the mean normal. The change, however, was transitory, and return to normal kidney function occurred in all except 4 patients during continuing sulfathiazole administration. In 2, the persisting low urea clearance could be explained by accompanying oliguria. That the comparatively moderate impairment of kidney function should be attributed to sulfathiazole seems doubtful, since other important contributing factors are known to be operative under these conditions.

Rough calculations of the clearances of free and conjugated sulfathiazole from data in Tables 1 and 2 showed little difference between the two forms. The average clearances of 8 patients presenting sufficiently high concentrations of the conjugated form to enable accurate measurement were 71 cc. of blood cleared per minute of the free, and 78 cc. per minute of the conjugated sulfathiazole. For sulfanilamide and sulfapyridine, Stewart, Rourke, and Allen<sup>12</sup> and Taylor and associates<sup>14</sup> found much lower values for the free forms, whereas clearances of the conjugated drug approximated those we have found for sulfathiazole. These observations imply that sulfathiazole is not reabsorbed as readily from the kidney tubules as are sulfanilamide and sulfapyridine.

In the presence of impaired kidney function, clearances of both free and conjugated sulfathiazole were lowered, the conjugated to a greater extent than the free.

Occasional specimens of urine of sulfathiazole-treated patients submitted for examination were opalescent and gave the impression that chylous urine was being secreted. Investigation showed this to be caused by a reaction between sulfathiazole or a derivative of



sulfathiazole and formaldehyde present as a preservative in one type of container used in this hospital.

6. *Toxic Effects.* Eighty-three patients suffering from pneumonia, including those listed in Table 2, have been observed for possible toxic manifestations. The incidence of untoward effects is shown in Table 3. In 4 patients nausea and vomiting were present before the start of sulfathiazole treatment, and in 2 these complaints followed the intravenous administration of sulfathiazole sodium. Unlike the severe and persistent vomiting caused by sulfapyridine, the vomiting induced by sulfathiazole was mild and infrequent and was marked by absence of severe nausea between attacks. In no case did nausea and vomiting necessitate discontinuance of therapy. Tabulated reports of the toxic effects of sulfapyridine recently published by some of the writers<sup>10</sup> and by Abernethy, Dowling, and Hartman<sup>1</sup> show a considerably higher incidence of vomiting when sulfapyridine was used.

TABLE 3.—TOXIC REACTIONS TO SULFATHIAZOLE (83 PATIENTS).

Nausea and vomiting:	Incidence.
Vomiting, 1 or 2 times . . . . .	7
more than 2 times . . . . .	1
Vomited before drug and continued after . . . . .	4
Hematuria, microscopic . . . . .	5
gross . . . . .	0
Dermatitis . . . . .	3
Psychosis* . . . . .	3
Leukopenia . . . . .	0
Acute hemolytic anemia . . . . .	0
Drug fever . . . . .	0
Agranulocytosis . . . . .	0

\* Two alcoholic patients, 1 senile hypertensive patient.

Dermatitis, apparently caused by the drug, was observed in 3 patients. Mental confusion was encountered in several patients, but in view of the severity of their illness, it was difficult to evaluate properly the rôle of the drug as the causative agent. Psychosis in 3 patients is to be explained by the presence of chronic alcoholism in 2 and advanced arteriosclerosis in 1. Repeated blood counts and hemoglobin determinations made during the course of drug administration failed to show evidence of any unusual depression in the number of the white or red blood cells or in concentration of hemoglobin. Urine studies showed no marked deviation from the usual findings for patients with severe febrile illness.

As already mentioned, crystals containing the drug were observed in the urine of 1 patient. However, sulfathiazole is much more soluble than sulfapyridine, so that hazard from precipitation in the urinary tract should be less when the former is used. Sulfathiazole did not seem to aggravate or increase the frequency of the cyanosis of pneumonia.

*Comment.* In case of absorption and excretion sulfathiazole resembles sulfanilamide. Because sulfathiazole is absorbed more

readily from the gastro-intestinal tract and excreted more rapidly than sulfapyridine, its use therapeutically is more easily controlled, an advantage that at times may be of decided importance. It is evident that sulfathiazole shows certain of the toxic effects described for other therapeutically active sulfonamido compounds. The toxic effects do not seem to offer any serious barrier to its use in treatment, and indeed in many ways toxicity appears to be less than that of sulfapyridine.

**Summary.** 1. The behavior of sulfathiazole has been investigated in 9 convalescent patients serving as controls and in 83 patients suffering from pneumonia.

2. Sulfathiazole is rapidly absorbed from the gastro-intestinal tract and is rapidly excreted in the urine. Following intravenous administration of the sodium salt, recovery of sulfathiazole in the urine is practically quantitative. It is not readily absorbed from the rectum.

3. The proportion of the drug conjugated is low in most individuals.

4. Effects observed on renal function and the hemopoietic system were transitory and not pronounced.

5. Vomiting occurred in about 10% of the patients treated with sulfathiazole, but was never severe enough to interfere with the use of the drug.

6. The incidence of other toxic reactions was small.

We wish to acknowledge the assistance of Miss Shlomith Bethlahmy, detailed for this and related studies on pneumonia by the Pennsylvania State Department of Health, Pneumonia Control.

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## BOOK REVIEWS AND NOTICES

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**CIRCULATORY DISEASES OF THE EXTREMITIES.** By JOHN HOMANS, M.D., Clinical Professor of Surgery, Harvard Medical School. Pp. 330; 29 text illustrations and 13 plates. New York: The Macmillan Company, 1939. Price, \$4.50.

In the last few years surgeons have interested themselves more and more in the circulatory diseases of the extremities. As the studies on the physiology of the sympathetic nervous system, lymphatics and the blood-vessels have been extended, a great deal of material relevant to clinical symptoms resulting from disorders of the circulation has accumulated. This material has been weighed and evaluated and the result is presented in an organized manner by the author.

Arterial diseases, arteriosclerotic deficiency, thrombo-angiitis obliterans, spasm of the arteries and embolism are clearly discussed so that there should be little confusion in the minds of those who carefully study these chapters on the differentiation of these disorders. In the same way he has presented diseases of the veins and lymphatics.

While surgical treatment is included the main object of the book is not to give detailed surgical technic but to present a complete picture of the diseases discussed so that this volume is of equal importance to the physician and surgeon.

The Reviewer feels that it is almost an impertinence to ask for anything more than this excellent work; but he believes that a general bibliography would be more helpful than the chapter references, where there is much overlapping of references. He would also suggest a more complete index. In the second edition there should also be a discussion of heparin as a therapeutic agent.

This book is of great importance and is recommended to every practitioner of medicine.

I. R.

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**OUTLINE OF PHYSIOLOGY.** By WILLIAM R. AMBERSON, Ph.D., Professor of Physiology, University of Maryland, and DIETRICH C. SMITH, Ph.D., Associate Professor of Physiology, University of Maryland. Pp. 412 (double column); 177 illustrations (15 in color), by NORRIS JONES, Instructor in Scientific Illustrating, Swarthmore College. Baltimore: The Williams & Wilkins Company, 1939. Price, \$4.00.

THIS text written by two teachers of the University of Maryland has recently been issued. It is admirably adapted for dental students, advanced college students and nurses, and might be used for collateral reading by students of medicine. Dr. Amberson has drawn upon his experience as a teacher in planning this text. At the outset some subjects, of a preliminary nature, are briefly but clearly discussed, the historical advances of the subject are briefly included, and the several phases of physiology are added. Although much of the detailed statements of larger texts are omitted, the basic facts of physiology are thoroughly discussed. Very few of the illustrations are from older texts. The illustrations and diagrams serve a definite purpose in following the descriptions in the text. It is an admirable text and the authors are to be congratulated upon its planning and completion.

B. McG.

PHYSIOLOGICAL CHEMISTRY. A Textbook for Students. By ALBERT P. MATHEWS, PH.D., Andrew Carnegie Professor of Biochemistry, The University of Cincinnati. Pp. 1488; 113 illustrations. Sixth edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$8.00.

THE new edition of this well-known text represents a serious attempt to bring the subject up-to-date since the publication of the previous edition in 1930.

The text is very readable and follows the author's bent in presenting the subjects with due emphasis upon historical development, and a characteristic tendency for a very personal imaginative appraisal of certain facts, their interrelationship and physiologic significance. Many teachers and students of the subject may prefer a much shorter text, and one much more objective in presentation. However, the choice of text is to an extent a matter of personal predilection, and some students no doubt are stimulated by an enthusiastic manner of presenting a subject.

The chapters upon Hormones, Vitamins and Mineral Metabolism are excellent. The love of the author for such terms as "cryptorrhetic" is excusable, but it denotes a tendency to pedantry which should not be encouraged in the student. In a sincere desire for historical approach, the author has erred in the use of relatively unreliable old data, when new precisely quantitative data could have been employed. For example, the absorption spectra of hemoglobin, as determined by the crude methods of Dhéré and Rollet (pages 781 to 784), may be cited. Such statements as "methemoglobin is a parahematin" (page 1004, footnote) is certainly misleading. The discussion of oxidation-reduction processes in the organism could have been improved materially if it were treated under a separate heading and the material upon the various oxidation-reduction enzymes had been included in this section.

D. D.

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SYNOPSIS OF PEDIATRICS. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief of the St. Mary's Group of Hospitals, assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine, and Assistant Pediatrician to the St. Mary's Group of Hospitals. Pp. 430; 144 illustrations. Third edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$4.00.

ANOTHER edition of this useful little book has been published. While the Reviewer feels that a standard textbook is best for the beginning student, he concedes that there is a place for a book of this type. It can be recommended for anyone reviewing for an examination, for interns and for the busy practitioner who desires concrete and accurate information.

Numerous revisions have been made in order to bring certain phases of the subject up to date and these additions are presented succinctly and accurately.

One wishes that the author had not adopted so whole-heartedly the Robertson hypothesis of growth, which though attractive is highly debatable. An outline of the maturation of the skeleton according to Todd and of the maturation of motor development according to Gesell would be helpful. Since the active immunization of children with certain vaccines is still debatable it might be well to have the author state his preference in the form of recommendations rather than positive statements.

The illustrations are clear and distinctive, and there is a satisfactory working index.

E. T., JR.

CLINIQUE ET PATHOLOGIE COMPAREE. Vénérologie—Cancérologie—Dermatoses—Médecine Générale—Phyto-Pathologie. By LOUIS BORY, Chef de Clinique de la Faculté de Médecine de Paris à l'Hôpital Saint-Louis, Prix Duchenne de Boulogne, 1937. Pp. 239. Paris: Masson & Cie, 1939. Price, Fr. 50 (paper).

THIS book is a pioneer in extending comparative pathology into the plant field. It is certainly most unusual in systematic relating such diseases as *lymphopathia venerea*, for example, on the lower animals. "Syphiloid of the cat" is another example. The book should have a particular appeal to dermatologists for its paragraphs on scabies, demodex infestation, urticaria and prurigos, eczema, neurodermites, keratoses, "trophodermies," leprosy, subcutaneous nodular tuberculosis of cattle, syphilis, syphiloid of the cat and lymphopathia venerea. Having general appeal are the tumors, the leucoses, John's disease, leprosy, subcutaneous nodular tuberculosis of cattle, infectious icterus and epilepsy.

Veterinarians, among others, must be interested in the special chapter which deals with diseases of animals which may be transmitted to him, but the medical profession at large can profit also from it. Diseases mentioned are as follows: glanders, anthrax, rabies, scabies, ringworm, variola, tetanus, aphthous fever, erysipeloid, foot rot and tuberculosis.

The chapter on phytopathology is particularly in point at this time when viruses are being energetically studied in plant materials and leaves the feeling that a fuller presentation would be welcomed. The author devotes 16 pages first to the general organization of plants and then to the lesions met in them. The "tumors" induced by *Bacillus tumefaciens* are included.

This long list of subjects is crowded into 236 pages, without any illustrations, consequently the treatment is so sketchy that the content is only suggestive. The average reader who is now led into a new and strange field must feel that the content is inadequate to a satisfactory knowledge of the situation. Footnotes carry references to the literature, which are only partly adequate; nevertheless the book is decidedly thought provoking by indicating avenues of approach through animals and plants to problems in human disease.

F. W.

OPHTHALMOLOGY. Vol. XX of *Clio Medica*. A Series of Primers on the History of Medicine. By BURTON CHANCE, M.D. Pp. 240; 6 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, \$2.00.

THIS is an epitome of the development of ophthalmology from antiquity to the present time. The first chapters deal with the treatment of diseases of the eyes by the Babylonians, Egyptians, Chinese, Arabians, Greeks and Romans. Then follow sections on the development of the science of ophthalmology up to the 19th century. The remaining chapters take up specific ocular disorders and trace the development of our knowledge of these up to the present. It is delightfully written by an authority on the history of ophthalmology.

F. A.

EYE, EAR, NOSE AND THROAT MANUAL FOR NURSES. By ROY H. PARKINSON, M.D., F.A.C.S., Head Oculist and Aurist to St. Joseph's Hospital, San Francisco, Calif. Pp. 243; 79 illustrations. Fourth edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$2.25.

A TEXTBOOK for nurses that contains excellent material, including diagrams covering the normal anatomy and physiology of the eye, ear, nose and throat and diseases of these structures, with very detailed instructions for the information of the nurse as to her responsibilities regarding treatment. The final chapter on "Public Health" describes the various

problems, in regard to these special conditions, that a nurse meets with in community nursing.

This book is the result of the author's belief that there is a need for it in the classroom and it has been written in the manner of classroom teaching, that is, in a conversational style, with considerable repetition and lack of clarity, as is natural in this form of writing. This is probably due to the fact that the author has written this book with his own immediate situation in mind; a better organization of the material would be a great improvement.

M. S.

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THE SURGERY OF INJURY AND PLASTIC REPAIR. By SAMUEL FOMON, PH.D., M.D., Formerly Major in Medical Corps, U. S. Army. Pp. 1409; 925 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$15.00.

THIS extraordinary book is reminiscent of the older German textbooks in that it includes a full discussion of all possible fields related to the surgery of injury and tissue repair. The first chapter is devoted to a general discussion of the operating room set-up, asepsis, suture material and instruments, the incision, hemostasis, etc. There are separate chapters on the fluid, salt and acid-base balance, on shock, anesthesia, preoperative management and postoperative management. Each of these chapters has a comprehensive table of references, although some of these have not been critically selected. An introduction of this character is so unusual that it deserves comment.

The chapters on plastic surgery are extensive, well documented and include practically every operation of any importance. It is regrettable that with a text of such importance the illustrations, which of necessity had to be limited in size, could not have been done throughout with ink. The pencil drawings when reproduced in such small size are fuzzy in outline and frequently obscure. A suggestion, which applies to a number of books on plastic surgery as well as to this one, is that all illustrations be placed in the same direction, that is, in illustrations of operations on the palate the nose should be toward the top of the page. It is unnecessarily confusing to have to orientate oneself for various positions of the palate.

Of all the textbooks on injury and plastic repair that have appeared, this is undoubtedly the most extensive, but, of even more importance, it is unique in its advocacy of the knowledge and use of physiologic principles in the treatment of patients.

This is a valuable book for the specialist and also for the general practitioner who is called upon to repair superficial injuries. It can be highly recommended.

I. R.

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MICROBIOLOGY AND PATHOLOGY. By CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas; Consulting Pathologist, St. Louis Southwestern Railway Hospital, Texarkana, Ark., and Mother Frances Hospital, Tyler, Texas, etc. Pp. 755; 165 illustrations and 25 colored plates. Second edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.25.

THE text is a brief but comprehensive survey of the fields of microbiology and pathology, in which bacteriology and related topics are emphasized. The section on microbiology has been thoroughly revised and broadened while the section on pathology remains essentially unchanged. The vast amount of material that is covered has necessitated the treatment of much of the subject matter in a definitive manner, while considerable space is devoted to the purely technical aspects of bacteriology and immunology. Generally, however, the subjects are presented in a simple, concise, factual

manner, and are supplemented with pertinent nursing suggestions, numerous illustrations, good references, an adequate glossary and index. Scientific nursing and its dependence upon an intimate understanding of the science of microbiology in relation to the nature of disease is emphasized throughout. A list of review questions covers each chapter and the section on microbiology is augmented by numerous simple and advanced laboratory exercises. The text is excellent from the standpoint of the graduate nurse or busy practitioner who wishes a sound, brief, easily readable and understandable reference to refresh and enlarge his basic understanding of disease; but is a bit too broad to be thoroughly grasped by the average student nurse in the time usually allotted for the study of these subjects. The noticeable variation in the density of the type will prove objectionable to the discerning reader.

H. H.

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**THE INFANT AND CHILD IN HEALTH AND DISEASE.** With Special Reference to Nursing Care. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., and ELIZABETH NOYES, R.N., Supervisor and Instructor of Pediatrics, Children's Hospital, San Francisco. Pp. 496; 140 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$3.00.

A TEXTBOOK for nurses, which is not lacking in information needed in caring for children. The normal infant and child are appropriately considered first.

Then their diseases are thoroughly considered in a well-written account, with 481 illustrations and 7 color plates. The nursing procedures are particularly valuable. This book is one of the best textbooks for nurses.

M. S.

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**THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE.** A University of Toronto Text in Applied Physiology. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (LOND.), F.R.S., F.R.C.P. (CANADA), Professor and Head of Department of Physiology; Associate Director of the Connaught Laboratories; Research Associate in the Banting-Best Department of Medical Research, University of Toronto, and NORMAN BURKE TAYLOR, M.D., F.R.S. (CANADA), F.R.C.S. (EDIN.), F.R.C.P. (CANADA), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Physiology, University of Toronto. Pp. 1872; 497 illustrations and 2 colored plates. Second edition. Baltimore: The Williams & Wilkins Company, 1939. Price, \$10.00.

FIRST published in 1937, and reprinted four times since then, this excellent book now appears in a new edition, thoroughly revised and including a large new section on the physiology of the special senses. Not only should students find it an ideal textbook, but physicians should welcome it as an excellent reference work to keep themselves abreast of modern concepts of physiology and the physiologic basis of scientific medical practice.

R. K.

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**ELECTROCARDIOGRAPHIC PATTERNS.** Their Diagnostic and Clinical Significance. By ARLIE R. BARNES, M.D., The Mayo Clinic, Rochester, Minn. Pp. 197; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

WRITTEN with the purpose of describing electrocardiographic patterns and pointing out their diagnostic importance in certain cardiac diseases, this monograph is not intended to furnish a complete discussion of electro-

cardiography. Thus nothing is said about the disturbances of cardiac rhythm.

The author is a seasoned veteran in clinical electrocardiography and for over 10 years has been one of the foremost investigators in this field. He is eminently qualified to prepare a monograph of this type. It is written in simple language and the thought is expressed clearly. The illustrations, an essential part of the monograph, are excellent. This sound, scholarly contribution should be in the library of everyone interested in electrocardiography. It will be particularly useful to the beginner and should be carefully studied by those who wish to qualify for the interpretation of electrocardiograms. It is a pleasure to recommend work of such high quality.

C. W.

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**ASTHMA.** By FRANK COKE, F.R.C.S. With the Collaboration of HARRY COKE, M.R.C.S., L.R.C.P., Honorary Physician, Charterhouse Rheumatism Clinic. Pp. 266; 19 illustrations. Second edition, fully revised and illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, \$4.00.

SIXTEEN years having passed since the publication of its first edition, a drastic revision of the book was obviously called for. This has been only partly achieved, for there remains much old material that is not in harmony with current views of this rapidly growing subject. The same may be said of some of the theoretical concepts propounded, such as aspirin sensitivity or the sedimentation test as sure criteria for the classification of the major types of asthma. Literary references are at times poorly chosen (as when the leukopenic index is attributed to another instead of to Vaughan). From the clinical angle there is much of practical value, notably the mode of use of vaccine therapy.

R. K.

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**INJURIES OF THE NERVOUS SYSTEM, Including Poisons.** By OTTO MARBURG, M.D., Clinical Professor of Neurology, Columbia University; Research Neuropathologist, Montefiore Hospital, New York, etc., and MAX HEFLAND, M.D., Assistant Clinical Professor of Neurology and Psychiatry, Columbia University; Chief of Nerve Clinic, Post-Graduate Hospital, New York, etc. Pp. 213; 16 illustrations. New York: Veritas Press, 1939. Price, \$3.00.

THIS comparatively short treatise comprises a wealth of information which is very important in view of the ever-mounting injuries resulting from traffic accidents. Marburg—formerly director of the Neurological Institute of the University of Vienna, now Clinical Professor of Neurology at Columbia University—reflects in almost every chapter the vast experience he had with injuries of the central and peripheral nervous systems during the World War. Even the seasoned neurologist will enjoy the comprehensive discussion of the symptomatology. In addition to the generally accepted characteristic signs of head and spinal cord injuries, one will find here a great number of the less known but very helpful methods of examination.

The practical viewpoint in diagnosis and treatment is stressed throughout. However, enough of the physiology and pathology is given to help the reader in the understanding of the symptoms and signs involved. Three photographs of macroscopic lesions and 13 well-selected photomicrographs from Helfand's investigations in vasomotor lesions in the brain following trauma are added. The general symptoms of head injuries and the special signs, diagnosis, pathology and treatment of concussion and contusion are discussed. The various forms of intracranial hemorrhages, of softening,



edema and cerebral atrophy, the fractures of the base of the skull and the injuries of the cranial nerves are described along with the neurologic sequelæ of concussion and contusion.

Five chapters deal with injuries of the spinal cord and the peripheral nerves, electric injuries, caisson disease and with trauma as the cause of organic nervous disease. The last chapter gives, in 10 pages, a concise résumé of the more common industrial intoxications such as lead, mercury, arsenic, thallium, manganese, benzol, benzene, carbon monoxide and carbon disulphide.

The importance and safeguards in evaluating pulse and blood pressure, the prognostic meaning of increase and decrease of body temperature, the value of pupillary disturbances as localizing signs, and the examination of the vasomotor system are discussed. The problems of traumatic necrosis and traumatic epilepsy are considered, and likewise, the percentages of partial and complete disability following the various kinds of injuries to the nervous system are considered at some length. The surgical treatment recommended for brain abscess, subdural hematoma, and traumatic epilepsy is at variance with the experience in this country. Some typographic mistakes and two errors in the labeling of the photomicrographs should be corrected in the next edition. The bibliography of over 300 references facilitates the orientation of the student.

The book is recommended as a short and valuable manual to internists, neurologists and surgeons, especially in the general hospital where a large number of head injuries are treated.

F. L.

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MANUAL FOR DIABETIC PATIENTS. By W. D. SANSUM, M.D., Chief of the Staff of The Sansum Clinic and Director of Metabolic Research of the Santa Barbara Cottage Hospital, ALFRED E. KOEHLER, Ph.D., M.D., Member of the Staff of The Sansum Clinic and Member of the Metabolic Research Staff of the Santa Barbara Cottage Hospital, and RUTH BOWDEN, B.S., Dietitian of The Sansum Clinic, Santa Barbara, Calif. Pp. 227; illustrated. New York: The Macmillan Company, 1939. Price, \$3.25.

In a book of this kind, written for patients, perhaps the greatest temptation is to write into the text the author's own methods of treatment as well as information of a technical nature which should be found only in medical textbooks. In this excellent little book the authors have almost entirely avoided both these pitfalls. The language is clear and the explanations specific, and the material is restricted to generally accepted principles and facts which will help the patient to a better understanding of his condition and of how to aid his doctor in its care; in fact, it could not be amiss to say that for the general information which it contains many physicians could read this book with profit. One-third of the book is taken up with tables of food values, substitutions, recipes and a short glossary. One feels that this book may with safety be put into the hands of almost any patient with the assurance that from it he can learn all that is essential and useful for his care.

R. R.

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THE HOSPITAL CARE OF NEUROSURGICAL PATIENTS. By WALLACE B. HAMBY, M.D., F.A.C.S., Associate Professor of Neurology and Instructor in Surgery (Neurological Surgery), University of Buffalo School of Medicine, Buffalo. Pp. 118; 24 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$2.00.

THIS compact little book fills a definite niche in our textbooks for teaching nurses and hospital internes. It is the first, short, condensed account of the problems met with in the preoperative and postoperative care of neuro-

surgical cases. The author has covered the field concisely but at the same time omitted nothing of importance.

The chapters on anatomy are particularly good, as they give in brief form all that a nurse needs to know on the subject. The chapters on technique and treatment are concise but sufficiently detailed for use in the training school and instruction in the operating room.

The Reviewer can recommend this book very highly to those who teach surgery to nurses. They should be thankful that the author has taken the trouble to bring this information together, so that it will no longer be necessary to look it up from a number of sources or to bring out elaborate technique sheets covering this subject.

F. G.

### NEW BOOKS.

*The Rise of Embryology.* By ARTHUR WILLIAM MEYER, Professor of Anatomy, Emcritus, Stanford University. Pp. 367; 95 illustrations. Stanford University, Calif.: Stanford University Press, 1939. Price, \$6.00.

*Mineral Metabolism.* By ALFRED T. SHOHL, M.D., Research Associate in Pediatrics, Harvard University (American Chemical Society Monograph Series). Pp. 384; 13 illustrations and 41 tables. New York: Reinhold Publishing Corporation, 1939. Price, \$5.00.

*Biological Products.* By LOUIS GERSHENFELD, P.D., B.Sc., Ph.M., Professor of Bacteriology and Hygiene, and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science, etc. Pp. 242; illustrated. New York: Romaine Pierson Publishers, Inc., 1939. Price, \$4.00.

*Lehrbuch der Augenheilkunde.* By DR. ERNST FUCHS, Sechzehnte, vermehrte und verbesserte Auflage neu bearbeitet von DR. ADALBERT FUCHS, a. o., Professor der Augenheilkunde an der Universität in Wien. Pp. 904; 362 text illustrations and 5 colored plates. Wien: Franz Deuticke, 1939. Price, Paper, M. 27; Bound, M. 30.

*Medicolegal & Industrial Toxicology, Criminal Investigation, Occupational Diseases.* By HENRY J. EILMANN, Ph.D., Director of Physicians' Laboratory Service of Toledo, Ohio; Lecturer in Bacteriology and Histology, Mary Manse College of Toledo. Pp. 324. Philadelphia: The Blakiston Company, 1940. Price, \$3.00.

*Medical Care (A Symposium). Law and Contemporary Problems.* Vol. VI, No. 4, Autumn, 1939 (A Quarterly Published by the Duke University School of Law, PROFESSOR DAVID F. CAVERS, Editor). Pp. 185. Durham, N. C.: Duke University Law School, 1939. Price, 75c.

*Principles and Practice of Aviation Medicine.* By HARRY G. ARMSTRONG, B. S., M.D., Captain, Medical Corps, United States Army; Director, The Aero Medical Research Laboratory, Air Corps Material Division. Pp. 496; 86 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.50.

*Unto the Fourth Generation. GONORRHEA AND SYPHILIS.* What the Layman Should Know. By IRVING SIMONS, B.S., M.D., Fellow of the American Urological Association; Fellow of the New York Academy of Medicine, etc. Pp. 243; illustrated (by M. EMANUEL, M.D.). New York: E. P. Dutton & Co., Inc., 1940. Price, \$2.50.

Apparently every publisher feels that he must have a book in a popular line on his publishing list, whether or not there is really need for such a book. One would be inclined to class this volume as just another "pop" presentation of the patient's side of venereal disease, its control and treatment; however, it has one outstanding feature, i. e., the space devoted to gonorrhea, the stepchild of the venereal disease control movement. The book is unlikely to reach more than a thin layer of the victims of venereal disease, whose reading contingent, is an insignificant part of the population strata involved in the problem. J. S.

*Congenital Cleft Lip, Cleft Palate and Associated Nasal Deformities.* By HAROLD STEARNS VAUGHAN, M.D., D.D.S., F.A.C.S., Professor of Clinical Surgery, New York Post-Graduate Medical School, Columbia University; Attending Surgeon, New York Post-Graduate Hospital, etc. Pp. 210; 259 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

*Beyond the Clinical Frontiers. A Psychiatrist Views Crowd Behavior.* By EDWARD A. STRECKER, A.M., Sc.D., Litt.D., M.D., Professor of Psychiatry in the Under-graduate and Graduate Schools of Medicine, University of Pennsylvania, and Consultant and Chief-of-Service, Institute of the Pennsylvania Hospital. Pp. 210. New York: W. W. Norton & Co., Inc., 1940. Price, \$2.00.

*Argyria. The Pharmacology of Silver.* By WILLIAM R. HILL, M.D., Instructor in Dermatology and Syphilology, University of Pennsylvania, and DONALD M. PILLSBURY, M.A., M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania. Pp. 172. Baltimore: The Williams & Wilkins Company, 1939. Price, \$2.50.

*The Inter-relationship of Mind and Body.* (The Proceedings of the Association, New York, December 27th and 28th, 1938). Editorial Board: FOSTER KENNEDY, ANGUS M. FRANTZ, CLARENCE C. HARE. Pp. 381; 28 illustrations and 10 tables. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.00.

*The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Age at Maximum Growth.* By FRANK K. SHUTTLEWORTH. (Vol. IV, Serial No. 22, No. 3.) *Evaluations of Adolescent Personality by Adolescents.* By CAROLINE McCANN TRYON. (Vol. IV, Serial No. 23, No. 4.) (Monographs of the Society for Research in Child Development.) Pp: No. 3, 291; No. 4, 83. Illustrations: No. 3, 150 and 110 tables; No. 4, 12, and 15 tables. Washington, D. C.: Society for Research in Child Development, National Research Council, 1939. Price, No. 3, \$2; No. 4, \$1.

*Fundus Atlas.* By LOUIS BOTHMAN, B.S., M.D., F.A.C.S., Clinical Professor of Ophthalmology, The University of Chicago; Associate Ophthalmologist, St. Luke's Hospital, Chicago, and REUEL W. BENNETT, Photographer for the Division of Ophthalmology, The University of Chicago Clinics. Pp. 50; Fifty original stereoscopic photographs. Chicago: The Year Book Publishers, Inc., 1939. Price, \$17.00.

*Atlas of Surgical Operations.* By ELLIOTT C. CUTLER, Mosley Professor of Surgery, Harvard University and Chief Surgeon of the Peter Bent Brigham Hospital; Formerly Professor of Surgery, Western Reserve University and Director of Surgery of the Lakeside Hospital, and ROBERT ZOLLINGER, Assistant Professor of Surgery, Harvard University and Senior Associate in Surgery at the Peter Bent Brigham Hospital. Pp. 181; 84 plates. New York: The Macmillan Company, 1939. Price, \$8.00.

*Medical Education in the United States, 1934-1939.* Prepared for the Council on Medical Education and Hospitals of the American Medical Association. By HERMAN G. WEISKOTTEN, M.D., Dean, Syracuse University College of Medicine, ALPHONSE M. SCHWITALLA, S.J., Ph.D., Dean, St. Louis University School of Medicine, WILLIAM D. CUTTER, M.D., Secretary, Council on Medical Education and Hospitals of the American Medical Association, HAMILTON H. ANDERSON, M.D., Member of the Staff, Council on Medical Education and Hospitals of the American Medical Association. Pp. 259. Chicago: American Medical Association, 1940. Price, \$1.00.

*Virus and Rickettsial Diseases with Especial Consideration of their Public Health Significance.* A Symposium held at The Harvard School of Public Health, June 12-17, 1939. Pp. 907; illustrated. Cambridge, Mass.: Harvard University Press, 1940. Price, \$6.50.

## NEW EDITIONS.

*An Introduction to Gastro-enterology.* Being the Third Edition of The Mechanics of the Digestive Tract. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, The Mayo Clinic, etc. Pp. 778; 186 illustrations. Third Edition. New York: Paul B. Hoeber, Inc., 1940. Price, \$10.00.

*A Textbook of Laboratory Diagnosis.* With Clinical Applications for Practitioners and Students. By EDWIN E. OSGOOD, M.A., M.D., Associate Professor of Medicine and Head of the Division of Experimental Medicine, University of Oregon Medical School, and Member of the Staff of Multnomah County Hospital, etc. Pp. 676; 27 illustrations and 9 colored plates. Third Edition. Philadelphia: The Blakiston Company, 1940. Price, \$6.00.

*Recent Advances in Neurology.* By W. RUSSELL BRAIN, D.M. (OXON.), F.R.C.P. (LOND.), Physician with charge of Out-patients to the London Hospital; Physician to the Maida Vale Hospital for Nervous Diseases; Neurologist to the Infants' Hospital, etc. Pp. 364; 24 illustrations. Fourth edition. Philadelphia: The Blakiston Company, 1940. Price, \$5.00.

This edition is largely rewritten and discussion of the following subjects is new, or nearly so: Pathogenesis and Treatment of Headache; Functions of the Frontal Lobe; Electro-encephalography; Vitamin Deficiencies in Relation to Nervous Disorders; Diseases Due to Neurotrophic Viruses; Use of Prostigmin in Myasthenia Gravis; Chemistry of the Muscular Dystrophies; Muscular Disorders Associated with Thyroid Disease, and the Treatment of Meningitis with Sulphanilamide. There are many references and an index. N. Y.

*Nomenclature and Criteria for Diagnosis of Diseases of the Heart.* By The Criteria Committee of the New York Heart Association, ARTHUR C. DEGRAFF, M.D., CLARENCE E. DELA CHAPELLE, M.D., CARY EGGLESTON, M.D., CHARLES E. KOSSMANN, M.D., ROBERT L. LEVY, M.D., JOHN B. SCHWEDEL, M.D., HAROLD E. B. PARDEE, M.D., Chairman. Pp. 282; 52 illustrations. Fourth edition. New York: New York Heart Association, a Division of New York Tuberculosis and Health Association, Inc., 1939. Price, \$2.00.

*Disorders of the Blood.* Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital; Late Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (New Zealand), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital; Pathologist, The Samaritan Free Hospital for Women; Late Assistant Pathologist, Christ Church Hospital, New Zealand. Pp. 603; 61 illustrations with 12 plates (8 colored). Third edition. Philadelphia: The Blakiston Company, 1939. Price, \$7.50.

It is not surprising that new editions of this excellent book are required every 2 years, especially if one realizes how rapidly hematology has been progressing in the past decade. One is more apt to get satisfactory and authoritative information on many subjects from this small book than from some of the larger works on the subject. "This edition contains important new matter concerning the hemolytic anemias, including more exact methods for the fragility test and for determining bilirubinemia, views concerning the technique and value of sternal biopsy as judged by our own experience, as well as modern opinions about certain of the hæmorrhagic states."

# PROGRESS OF MEDICAL SCIENCE

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## PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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### STAPHYLOCOCCUS TOXIN; A RÉSUMÉ.

**I. Introduction.** It would seem appropriate at this time to review the problem of the production, preservation and the pathologic lesions produced by staphylococcus toxin. Recent observations indicate that this toxin and the toxoid and antitoxin prepared with it are not only of scientific interest but they are assuming clinical significance.

Both French and German investigators began the study of staphylococcus toxin following the observations of Billroth<sup>6</sup> and Koch<sup>49</sup> on this bacterium. Many publications appeared between 1874 and 1908. Relatively few papers appeared between 1908 and 1925.

Interest in the staphylococcus and its toxin was revived following the Brundenberg disaster which occurred in Australia in 1928.<sup>16</sup> At that time a group of 21 children were given diphtheria toxin-antitoxin and 12 died within the following 24 hours. A British Royal Commission investigated this disaster and found that the antigen was contaminated with *Staph. aureus*. The children died apparently from an acute intoxication, no doubt resulting from this staphylococcus. Abscesses formed at the site of inoculation in each of the 9 children who survived. A staphylococcus was isolated from these lesions similar to that present in the toxin-antitoxin used for the inoculum. The results of this disaster stimulated both clinical and experimental studies on the staphylococcus and its toxin particularly in England and in America.

Burnet<sup>14a,b,c</sup> in Australia, Dolman<sup>24a</sup> in Canada, and Parker<sup>72-74,98</sup> in the United States, made several important contributions pertaining to staphylococcus toxin between 1925 and 1932. In 1929, Burnet<sup>14a</sup> first prepared staphylococcus toxoid by treating staphylococcus toxin with formaldehyde. The experimental and clinical use of this staphylococcus antigen immediately attracted the attention of investigators. Dolman deserves credit for the early observations on the clinical use of this antigen. More recently, the French have made many clinical studies with staphylococcus toxoid and antitoxin.

The early workers on staphylococcus toxin thought that it contained

several different fractions. Those most frequently discussed were leuko-  
cidin, hemolysin, acute killing fraction, skin necrotizing fraction and  
nephrotoxin.

**II. Production of Staphylococcus Toxin.** The production of toxin by  
the staphylococcus is influenced especially by the medium and the  
duration of growth. Attempts to determine the best medium for the  
production of toxin have resulted in a considerable number of experi-  
mental studies. One of the earliest of these media was veal bouillon  
used by de Christmas<sup>18</sup> in 1888 to obtain the toxin which he injected  
into the anterior chamber of a rabbit's eye. It induced edema and sup-  
puration. Van de Velde<sup>23</sup> grew staphylococci in blood, serum and  
bouillon to demonstrate the effect of the filtrate on leukocytes. He  
showed the presence of a substance which destroyed leukocytes.

Neisser and Wechsberg<sup>62</sup> in 1901 apparently were the first to give  
considerable attention to the conditions under which staphylococcus  
toxin is formed. Meat infusion broth was their basic medium. This  
has continued until the present to be basic in the preparation of staphy-  
lococcus toxin. Bigger<sup>5</sup> and his co-workers in 1927 were the first to  
digress from liquid media for the production of toxin. They grew the  
cocci on an agar surface and washed them off with saline to obtain the  
toxin. The medium used at present for the production of staphylococcus  
toxin is a modification. The proportions of ingredients are such now  
that a semisolid medium is usually formed.

McIlwain<sup>55</sup> has recently studied the effect of agar on the production  
of alpha hemolysin. His observations show that the production of  
toxin in a chemically defined medium is reduced by the calcium in the  
agar and that it is increased by the remainder of the agar molecule.  
The stimulating properties of agar are not due to its sulphuric ester  
grouping but to the polysaccharide residue. Agar in the medium used  
for the production of staphylococcus toxin may act by absorbing meta-  
bolic products deleterious to the production of the toxin.

Holt,<sup>40</sup> in 1936, studying the conditions under which staphylococcus  
toxin is formed, divided the nutritional elements in a beef-juice medium  
into large and small molecules by either saturation with ammonium  
sulphate to obtain the former or by dialysis to get the latter molecules.  
The yield of toxin in the "dialysate medium" and in the undiluted  
dialyzed medium was usually identical but the growth of bacteria was  
much greater on the latter.

Many substances have been added to the basic medium in an attempt  
to increase the production of toxin. Different preparations of peptone  
apparently have little influence on the amount of toxin that is formed.  
Walburn<sup>96a,c</sup> concluded from his studies that a 1% solution was the  
minimum in which staphylococci would grow and produce a lysin. An  
albumin, according to Walburn, is not an important factor for the  
growth of staphylococci and the formation of toxin. Glucose in a 1%  
concentration prevents the production of toxin.<sup>96c</sup> Parker<sup>72</sup> thinks that  
toxin only appears later when the medium contains a trace of glucose  
and that it probably does not appear until the sugar is destroyed.  
Certain salts such as calcium and sodium either partially inhibit or  
completely prevent the formation of staphylococcus toxin.<sup>98</sup> Salts of  
manganese, nickel, magnesium, and potassium when added to the

medium promote the formation of toxin. The rôle played by these salts is not understood. It would appear that some may act as "buffers."

Neisser and Wechsberg<sup>62</sup> and Walbum<sup>96c</sup> have considered the importance of "buffers" in the growth of staphylococci and the production of toxin. The latter found that the maximum amount of toxin was produced at pH 6. Other investigators, however, produce good toxin in a more alkaline medium. Hemolysins are present at a pH of 8-9. Burnet<sup>14b</sup> buffered his medium by placing it in a McIntosh and Fildes anerobic jar and replaced 10 % of the air with carbon dioxide. Subsequent observations indicate that 20 % carbon dioxide in 80 % oxygen is a better buffer than 10 % carbon dioxide alone.

The length of time required for the staphylococci to grow and produce the maximum amount of toxin is influenced by several factors. One of these is the temperature. Walbum<sup>96c</sup> found the best to be around 40° C. The maximum amount of toxin is formed after 2 to 3 days. Some investigators in producing toxin have grown their cultures for 9 to 13 days. More recent experiments would indicate that 48 hours is a sufficient incubation time at 37.5° C. for the production of toxin. There may be some deterioration of the toxin when the cultures are incubated for several days.

Staphylococcus toxin is separated from the medium by filtration. The filters more frequently used are the Berkefeld, Seitz and Chamberland. Burnet<sup>14b</sup> observed that filtration through a Seitz did not affect the hemolytic titer appreciably. Personally, I was unable to determine any difference in the amount of hemotoxin before and after filtering a large quantity of a culture of staphylococci grown in a semisolid medium through a Berkefeld V candle. Nélis<sup>63</sup> noted that the enterotoxic substance in staphylococcus cultures was retained by an L<sub>2</sub> filter but it did pass a Seitz.

The choice of a method for filtering staphylococcus toxin is influenced by the constituents in the medium. The cultures can be centrifuged to eliminate many of the large particles before they are filtered. When agar has been used in the medium it is much better to filter before the culture becomes chilled.

Many efforts have been made to purify and concentrate staphylococcus toxin. The results apparently have not been as encouraging with staphylococcus as they have been with tetanus and diphtheria toxin. Bigger<sup>5</sup> and his associates were able to dry the supernatant fluid obtained from washing the surface of agar slants by placing it in a petri dish and keeping it at 37° C. overnight. The residue was a yellow film with a rather rancid odor which could be reduced to a powder form. When water, equivalent to the amount of liquid evaporated, was added, a cloudy fluid formed which was as active in producing hemolysis as the original filtrate. The dry lysin was very stable. The toxin could be concentrated by this method. Burnet and Freeman<sup>15</sup> precipitated staphylococcus toxin with either alcohol or ether in the cold and adsorbed the precipitate on aluminum hydroxide. The toxin was released with either Rochelle salt or a weakly alkaline solution. Staphylococcus toxin can also be precipitated with acetic acid. A yield of 60 to 90 % has been obtained by this method. The bulk of the nitrogenous constituents in the crude toxin were also removed. When the latter method

of purification is used there is an increase in the units of toxin per milligram of nitrogen. This experiment indicates that the toxin has no definite relation to the amount of nitrogen in any single preparation. Only a small part of the acid precipitate consists of toxin; metaproteins, nucleo proteins and other acid precipitated nitrogen compounds constitute the greater part of the precipitate.<sup>15</sup>

Holt<sup>40</sup> concentrated staphylococcus toxin as follows: the filtrate was saturated with ammonium sulphate and centrifuged. The supernatant liquid was discarded and the precipitate was redissolved in water. By this method 90 to 98% of the toxin was recovered. When concentrated and purified as above, the toxin is said to be more stable than the raw material. The antitoxin-binding and hemolytic powers remain constant for many months, indicating according to Holt that very little or no autotoxoiding action takes place.

Most investigators have not only been interested in determining the type of medium and the environmental conditions under which the staphylococcus produces the most toxin, but they have also been interested in determining the mechanism of the formation of this toxin. At present the chemical composition of staphylococcus toxin as well as that of other toxins is not known. Recent experiments have shown several interesting factors about the formation of this toxin and they indicate that additional information along this line may give pertinent data pertaining to the composition of staphylococcus toxin. Knight<sup>48</sup> found that the accessory substances necessary for the growth of staphylococci were either nicotinic acid and vitamin B, or closely related substances. Toxin has not been produced in significant amounts until recently in a synthetic medium. Gladstone<sup>34</sup> has published a paper on "The Production of Staphylococcal Alpha-Hemolysin in a Chemically Defined Medium." In this paper the different constituents in the medium are discussed as well as the environmental conditions under which staphylococcus toxin is formed. With the knowledge of the growth requirements of the staphylococcus, studies on synthetic media may reveal important facts about the formation and composition of this toxin.

Holt<sup>40</sup> has obtained growth and produced toxin in a medium made with the dialysate from nutrient broth. McClean<sup>56</sup> observed that agar added to broth enables the staphylococcus to produce a potent toxin. I have made similar observations on the use of agar in media and have also found that gauze cut into small pieces and added to veal infusion broth enhanced the production of toxin. Cellophane, according to McClean,<sup>56</sup> exerts some influence on broth which renders it suitable for the production of toxin. These observations made with agar, gauze and cellophane on the production of toxin suggest the possibility that adsorption may enter the process of toxin formation, but nothing specific as to the composition of toxin, however, has been determined.

Eaton<sup>28</sup> has stated very appropriately, I think, that a constituent of the medium need not necessarily act directly either by stimulating growth or increasing the toxigenicity of the culture. It may act either by removing an inhibitory factor, by effecting changes in pH, reducing conditions during growth, or by protecting the formed toxin from destruction. Traces of unknown impurities in an "essential" substance



may even stimulate the formation of toxin. There is evidence, according to Eaton, to support the idea that toxins are synthesized in the bacterial cells and then either liberated by diffusion or by disruption of the cells. Eaton, in discussing staphylococcus toxin, states that it is possible that the enterotoxic substance present in cultures of staphylococci is a metabolite and not a true toxin.

**III. Preservation of Staphylococcus Toxin.** Staphylococcus toxin, like other bacterial toxins, deteriorates spontaneously. The rate at which it loses its toxicity is much slower, however, than that of diphtheria. Oxidation and reduction may play a rôle in the spontaneous deterioration of staphylococcus toxin. Apparently no one has determined whether or not staphylococcus toxin is antigenic following this form of deterioration.

Bigger<sup>5</sup> and his co-workers found that dry staphylococcus lysin was very stable. A sample kept at cold-room temperature in a desiccator for 2 months had exactly the same titer as when it was fresh. Filtrates preserved in the ice-box also do not lose their potency as rapidly as when kept at room temperature. Jordan and his associates found that staphylococcus toxin retained the original strength for at least 3 to 4 weeks when kept cold.<sup>44</sup> All observations on the spontaneous deterioration of staphylococcus toxin, however, have been made over periods too short for the data to be of much significance.

Staphylococcus toxin deteriorates very rapidly when highly diluted with physiologic saline. It is of interest to note that the hemolysin and the skin necrotizing factors both are affected similarly by this diluent. Burnet<sup>14c</sup> observed that staphylococcus toxin deteriorates much less rapidly in infusion broth than in saline. This toxin also deteriorates at different rates when diluted with saline and infusion broth extracts of different rabbits' tissues.<sup>81</sup> Regardless of all the observations on staphylococcus toxin, little is known of the mechanism of deterioration.

Many observations have been made on the effect of heat on staphylococcus toxin. Frequently the data are very meager, yet, all the experiments show that it is destroyed by heat. The amount of heat required to completely inactivate staphylococcus toxin, according to Gengou,<sup>33</sup> is influenced by the pH of the filtrate. The differences in pH may account for the wide range of temperatures which have been recorded as being necessary for the complete inactivation of staphylococcus toxin. A detailed study of the effect of heat on the hemolytic and skin necrotizing factors in staphylococcus toxin has recently been reported by Rigdon.<sup>79j</sup> It was found that the rate of deterioration is influenced both by the length of time at which the toxin is heated and the temperature. Toxin heated at 45° C. for 2 hours loses approximately 9% of its hematoxin, while the same toxin heated at 54.03° C. loses over 99% of its toxicity during the same period. Toxin heated for 2 hours at 57° C. still shows a trace of the hemolysin. The nature of the change induced by heat is not clearly understood.

Staphylococcus toxin is detoxified through the action of certain chemicals and it may or may not be antigenic. Burnet<sup>14a</sup> was the first to completely detoxify staphylococcus toxin with formaldehyde. The binding power of this treated toxin toward antitoxin is retained up to

about 50% of the initial value and the flocculation titer is practically unaltered.<sup>15</sup> *Staphylococcus toxoid* is an effective antigen capable of provoking high titer antitoxic sera in rabbits. The concentration of formaldehyde, the pH of the reaction and the temperature all influence the rate of detoxification. The loss of primary toxicity according to Burnet follows an approximate monomolecular course, *i. e.*, when the logarithms of the hemolytic titers are plotted against time a curve is obtained which approaches a straight line. It would appear therefore, according to Burnet,<sup>15</sup> that formaldehyde acts directly on the toxic groups without affecting other parts of the toxin molecule which are concerned only with antigenicity and combining activity.

Strong acids and alkalis destroy *staphylococcus* toxin very quickly.<sup>63</sup> There is little data to indicate that toxin thus treated is either antigenic or that it retains its combining power for antitoxin. Benzoate, sodium tartrate and lactic acid, according to Nélis, produce only a minimum detoxifying action on *staphylococcus* toxin, while salicylic, benzoic and especially *B. oxynaphtholic* acids produce a much greater detoxification.

*Staphylococcus* toxin is detoxified by shaking it with either chloroform or ether. In this method an equal volume of ether is added to *staphylococcus* toxin. The mixture is placed in a sealed tube and mechanically shaken. After a period of 10 minutes the toxin contains only 32% of the original amount of hemotoxin. When similarly treated for 48 hours only 0.46% is demonstrable. *Staphylococcus* toxin thus treated with chloroform is a very poor antigen. Johlin<sup>41</sup> thinks that the process of detoxification of *staphylococcus* toxin with both chloroform and with ether is one of interfacial adsorption. The effects produced by this surface adsorption are undoubtedly that of the catalytic action of surface concentration and orientation.

Li<sup>53</sup> was able to remove completely the hemolytic, dermonecrotic and lethal properties of *staphylococcus* toxin by the combined action of methylene blue and light. The toxin thus treated was equal in antigenicity to formol-toxoid and alum precipitated formol-toxoid. This method of detoxification is especially interesting since it is considered to be one of oxidation.

**IV. Relation Between the *Staphylococci* and the Production of Toxin.** The relationship between the cultural characteristics of *staphylococci* and the production of toxin has been frequently studied since Ogston,<sup>68</sup> in 1882, first suggested a classification for this bacterium. It was recognized very early that *staphylococci* from pyogenic foci produce pigment. This gave rise to the separation of the organism into the aureus and albus groups.

Neisser and Wechsberg<sup>62</sup> were among the first to note a variation in the amount of toxin produced by certain strains of *staphylococci*. Those isolated from carbuncles and deep seated foci of inflammation in the human were usually toxin producing strains. *Staphylococci* isolated from animals may produce toxin. Minett<sup>59</sup> found that *staphylococci* isolated from suppurative processes in dogs may produce a toxin which is highly active against sheep red corpuscles but inactive against rabbit red blood cells. This and other observations indicate that the hemotoxin produced by different strains of *staphylococci* may be different.

The type of hemotoxin produced by *staphylococci* apparently is

influenced by the environmental conditions under which the organisms have been growing and also the medium in which the bacteria are grown for the production of toxin. These factors have not always been considered in the studies on the type of hemotoxin produced by different cultures of staphylococci. Some of the observations on Beta toxin have been made with organisms isolated from animal sources.<sup>59</sup>

There appears to be no relationship between the quantity of toxin produced by the staphylococcus and the virulence of the organism for man. Recent observations suggest, however, that there may be some relation between the amount of hemotoxin necessary to lyse rabbit red cells and the virulence of the organism for the rabbit. Timmerman<sup>61</sup> has recently called attention to the variation in the susceptibility of red cells from different rabbits to staphylococcus toxin. I have also observed such a variation in rabbits' red cells. The difference in the susceptibility of red cells from different animals for toxin and the variation in the susceptibility of different animals for staphylococci has made it difficult to correlate toxin production and pathogenicity. Furthermore, to add to the complexity of this problem Bigger<sup>4</sup> has noted that the amount of toxin produced by any staphylococcus is not always constant.

It is well known that the cultural characteristics of the staphylococcus are variable. At present it is questionable whether or not there is any relationship between the ability of an organism to produce toxin, its virulence and its pathogenicity. McBroom<sup>64</sup> states, however, that hemotoxin production in staphylococci is definitely correlated with the extent and the speed of reduction of methylene blue to the leukobase.

**V. Staphylococcus Coagulase and Fibrinolysin.** Staphylococcus-coagulase is more frequently encountered in broth cultures of staphylococci although it does occur sometimes in certain of the staphylococcal filtrates.<sup>29a</sup> The association of the toxin and the coagulase is interesting.

The phenomenon of the clotting of blood by staphylococci or by the products of these organisms was first mentioned by Delezenne in 1898.<sup>21</sup> Many observations have been made since that time on the clotting of plasma by staphylococci or their filtrates. Gratia<sup>37</sup> and Gross<sup>38</sup> obtained the coagulase free from the bacteria by filtering a broth culture of staphylococci. The substance is sometimes heat stable; usually it is heat labile.<sup>29</sup> Gross considers it antigenic while Sudhues and Schimrigh<sup>90</sup> and Fisher<sup>29a</sup> thinks that it is non-antigenic.

The action of this coagulase on plasma is similar to that of an enzyme.<sup>19</sup> It may or may not be present in filtrates containing staphylococcus toxin.<sup>17,19</sup> This coagulating substance appears in broth cultures within the first 3 days of incubation.<sup>29</sup> It can be precipitated from the filtrate with alcohol and concentrated in saline.<sup>29</sup> Coagulase is a substance elaborated by the staphylococcus. It is most closely correlated with the pathogenicity of this organism for the rabbit, according to Cruickshank<sup>19</sup> and others.<sup>17</sup>

The phenomenon of fibrinolysis and the effects produced by the plasma-coagulating substances should be considered along with a discussion of broth cultures of staphylococci. Filtrates, however, may sometimes contain it.<sup>29b</sup> Aoi<sup>2</sup> found that fibrinolysin resists heat (100° C. for 1 hour), direct sunlight and many antiseptics. It occurs

with greatest regularity in 5 to 14-day-old cultures.<sup>29b</sup> It may be precipitated with either 75 % alcohol or acetone and it is antigenic.<sup>29b</sup>

Madison<sup>57</sup> found that 77 % of the 78 strains of staphylococci isolated from superficial human infections had no fibrinolytic function, whereas 90 % of 30 strains from "internal" human lesions were fibrinolytic. Fisher<sup>29b</sup> says that the fibrinolytic property of the staphylococcus appears to be inseparable from the live organisms in 24 out of 26 cases studied. Apparently staphylococci elaborate this substance according to Fisher as they grow in the clot. Some of the best plasma-coagulating strains show no coagulating activity toward fibrinogen. Fisher thinks that this may mean that either there is some substance in plasma and not in fibrinogen which aids in coagulation or that staphylococci may dissolve the fibrinogen before they clot it.<sup>29b</sup>

Our present knowledge is meager about staphylocoagulase and the fibrinolytic properties of staphylococcus filtrates. It can be said, however, that these substances are primarily two different things and that both are different from staphylococcus toxin. Aoi<sup>2</sup> reports that three reactions of the staphylococcus, the hemolysin, the coagulase and the fibrinolysin are intimately connected with the pathogenicity as determined by skin tests on rabbits.

Neter<sup>66</sup> has recently studied the fibrinolytic, anticoagulating and plasma-clotting properties of staphylococci. He found that the fibrinolysin dissolves human as well as animal plasma clot. Furthermore, it can be specifically neutralized by staphylococcus antiserum. The relation of the fibrinolytic, anticoagulating and plasma-clotting properties to the toxin produced by the staphylococcus was not considered, however, by Neter.

**VI. Pathologic Lesions.** De Christmas,<sup>18</sup> in 1888, apparently was the first to observe the local effect of staphylococcus toxin on any tissue. Acute conjunctivitis developed following an injection of it into the anterior chamber of a rabbit's eye. Conjunctivitis<sup>1</sup> may even occur when the toxin is instilled into the eyes of both human beings and experimental animals. Allen<sup>1</sup> has recently shown that a keratoconjunctivitis may also occur following the local injection of staphylococcus toxin into the eye. The lesion produced by staphylococcus toxin, according to Allen, is similar to that so frequently found in clinical cases of staphylococcus conjunctivitis.

Staphylococcus toxin when injected subcutaneously produces local necrosis. Von Lingelsheim,<sup>95</sup> in 1900, apparently was the first to produce this lesion in the skin of the rabbit. Since that time it has been frequently described. Parker,<sup>72</sup> in 1924, gave the histologic changes in the rabbit's skin following the local injection of this toxin. Recently I have studied the lesions produced by staphylococcus toxin in the subcutaneous tissue of mice.<sup>79a</sup> They are characterized by necrosis of all the tissue in the area. It is interesting that there are very few leukocytes present during the first 3 hours following the injection of staphylococcus toxin. This may indicate that leukocytes either do not reach the zone or that these cells are destroyed immediately by the leukocidic action of the toxin. After 3 hours apparently all the toxin has either united with the tissue or has been removed by the lymph and blood.

Leukocytes have invaded the area of necrosis at this time and apparently they are very active in phagocytosing the débris.

A potent preparation of staphylococcus toxin usually produces injury when injected into any tissue. Recently the lesions produced by this toxin when injected through the patella into the knee joint of rabbits were described.<sup>79c</sup> The acute process is characterized by edema and hyperemia of the periarticular tissues accompanied by a small amount of bloody fluid in the joint cavity. This acute reaction slowly subsides and there develops a chronic reaction accompanied by a proliferation of fibrous tissue around the joint. The cartilage of the ends of the bones may become eroded.

Focal areas of necrosis in the colon is another lesion that follows the local injection of staphylococcus toxin in the dog.<sup>79d</sup> The wall of the colon is edematous, and hyperemic 24 hours after the local injection of staphylococcus toxin. The mucosa is necrotic and areas are sloughing at this time. The lumen of the glands in the mucosa are frequently filled with degenerated epithelial cells and débris. The epithelial cells lining these glands show all degrees of injury from cloudy swelling to coagulation necrosis during the first 24 to 36 hours. The edema decreases considerably by the second to the fourth day following the injection of the toxin. Ulcers are present in the mucosa at this time. The margin and base of these ulcers are irregular and the adjacent tissue is infiltrated with leukocytes. Regeneration of the mucosa apparently begins very early and after 9 days many of the ulcers are covered by new epithelium.

Necrosis occurs in the brain of the dog in the areas injected with staphylococcus toxin.<sup>79i</sup> A similar lesion is produced by the same quantity of infusion broth injected into the brain of the same animal. In view of the latter lesion it would seem more likely that the necrosis following the local injection of staphylococcus toxin is due to trauma rather than to the direct action of staphylococcus toxin on brain tissue. Collections of red blood cells infrequently occur around the small blood-vessels in the cerebral cortex following an intravenous injection of staphylococcus toxin in the dogs. These collections of red cells are similar to other lesions which occur in the dog following the intravenous injections of this toxin.<sup>79a</sup>

Pathologic lesions occur following the oral administration of staphylococcus toxin. The association of staphylococci with certain cases of food poisoning makes the significance of this route very important. Borthwick<sup>9</sup> has introduced staphylococcus toxin into the stomach of laboratory animals. The animals died at intervals varying from 2 minutes to 5 days. Intense congestion of the mucosa of the stomach and duodenum associated with small hemorrhages in the tissue and effusion of blood into the lumen, congestion and hemorrhages in various internal organs constituted the most important postmortem lesions.

Borthwick<sup>9</sup> discusses the effect of the gastric secretions on staphylococcus toxin. His experiments indicate that this toxin can be absorbed through the intestinal mucosa of the rabbit and guinea pig. The sensitivity of staphylococcus toxin to slightly acid and alkaline reactions is of special interest in considering the frequency of the occurrence of staphylococcus food poisoning in the human.

Lesions have been frequently observed in the different viscera following the intravenous injection of staphylococcus toxin.<sup>79a,l</sup> The production of these lesions have been attributed to specific fractions in the filtrate. Van de Velde,<sup>93</sup> in 1894, first observed that leukocytes were destroyed by staphylococcus toxin. He gave the name leukocidin to that fraction in the toxin which destroyed these cells. A leukopenia develops following multiple intravenous injections of staphylococcus toxin in the rabbit.<sup>46</sup> Young myeloid cells appear in the circulating blood of these animals provided they survive the acute effects of the toxin for 36 hours or longer. The femoral bone marrow is hyperplastic in these animals if they live for 3 days or longer.<sup>79l</sup> These new cells appear to be of the myeloid series. Rabbits given staphylococcus toxin intravenously and dying within 24 to 48 hours usually show only focal areas of necrosis in the bone marrow. From these observations it would seem that staphylococcus toxin may destroy leukocytes both in the bone marrow and in the circulating blood.

Neisser and Wechsberg<sup>62</sup> introduced a method to study the effect of toxin on white blood cells. It was based upon the fact that living leukocytes reduce solutions of methylene blue. The method is particularly adaptable for quantitative studies.

Staphylococcus toxin may effect the erythroblastic series of cells as well as the myeloid following an intravenous injection. This was first noticed by Denis and Van de Velde<sup>22</sup> in 1895 and Kraus and Clairmont<sup>50</sup> in 1900. Since that time the action of staphylococcus toxin on red blood cells has been frequently studied in an attempt to learn something of the mechanism of hemolysis.

Kraus and Pribram,<sup>51</sup> in 1906, observed that certain filtrates of broth cultures of staphylococci kill rabbits in 5 to 30 minutes following an intravenous injection. Similar results have been obtained by others following the injection of staphylococcus toxin. The lethal factor has been applied to that substance in the filtrate responsible for this acute death.

Neisser and Levaditi,<sup>61</sup> in 1900, described areas of necrosis in the cortex of rabbits' kidneys following the intravenous injection of staphylococcus toxin. Nephrotoxin is the term applied to the fraction in the staphylococcus filtrate responsible for the production of this renal lesion. Similar areas of necrosis have been described by others in the kidneys of rabbits, cats and dogs.<sup>32,36,79m,94</sup>

Neisser and Levaditi<sup>61</sup> thought that these cortical necroses resulted from the occlusion of blood-vessels in the kidney by emboli; furthermore that these emboli were formed by groups of leukocytes which had been destroyed through the action of the leukocidin present in the same toxin. Rigdon, Joyner and Ricketts,<sup>82</sup> in 1934, expressed the opinion that this renal lesion resulted primarily from the direct action of staphylococcus toxin on the cells in the kidney. Glynn<sup>36</sup> more recently has shown that the mitochondria in the tubular epithelial cells of rabbits show evidence of injury within 5 minutes following an intravenous injection of staphylococcus toxin.

Focal areas of hemorrhage and necrosis have been observed following the intravenous injection of staphylococcus toxin in the gastro-intestinal

tract, heart, pericardium, lungs, liver, adrenals, mesentery, spleen, diaphragm and bladder.<sup>79a,1</sup>

The many lesions produced by staphylococcus toxin apparently have led to diverse opinions on the mechanism of the action of this toxin. There are several well established terms that are used at present to denote specific fractions in the toxin. Many attempts have been made to prove that these fractions are either the same or different substances. Much of the work of the early investigators supports the theory that staphylococcus toxin is composed of multiple fractions. Recent experiments, however, indicate that the toxin may not be so complex.

Neisser and Wechsberg<sup>62</sup> considered the leukocidin as a substance different from the hemolysin. Their experiments showed, however, that some leukocidin was adsorbed on red blood cells along with the hemolysin. Furthermore, the hemolysin as well as the leukocidin decreased when a filtrate was put with leukocytes. Another factor which indicates that the hemolysins and leukocidins are not the same substance is that antibodies for the leukocidin are produced in an animal immunized with only a lysin containing filtrate.

Wright<sup>100</sup> examined the filtrates prepared by the method of Parish and Clark from cultures of staphylococci of pathologic and non-pathologic origin, and found that alpha hemolysin and leukocidin as determined by the Neisser and Wechsberg technique were identical. Panton and Valentine,<sup>69</sup> using human neutrophils, found a leukocidin different from alpha hemolysin. Proom<sup>75</sup> has studied the relationship of the Neisser and Wechsberg type of leukocidin to the Panton-Valentine type and to alpha hemolysin. It appears from the latter's observations that the method of preparation of the toxins is of fundamental importance. Leukocidin may be present in filtrates from young cultures of certain strains of staphylococci which may not produce high alpha hemolysin. Both the alpha hemolysin and the Panton-Valentine leukocidin destroy the respiratory powers of the rabbit's neutrophils.

Weld and Gunther<sup>98</sup> state that they were able to adsorb on red cell stroma the substances responsible for sudden death, the renal lesion, hemolysis and the leukocidin. Nine-tenths of the hemotoxin and leukocidin was removed by the stroma, leaving the necrotoxin undiminished in the filtrate. It would appear unwise to conclude too much from this experiment in view of the wide variation in the susceptibility of rabbits to staphylococcus toxin; and furthermore Weld used only 2 rabbits to test the stroma absorbed filtrate.

Flaum and Forssman,<sup>31,32b</sup> in one of their many studies on staphylococcus toxin, absorbed the hemolysin on sheep red blood cells. Recently I titrated the hemolysin in a single preparation of toxin, using a 1% suspension of rabbit and sheep red cells, and found that the latter cells were not lysed by a low dilution of the toxin. After being in contact with sheep cells for 18 hours this concentration of toxin when placed with rabbit cells lysed them approximately the same as the toxin that had not been in contact with sheep cells. The results of the latter experiments indicate that either the toxin used was not adsorbed on the sheep cells or that a specific hemolytic fraction for these cells was adsorbed but that it was in a concentration too small to hemolyze the sheep cell.

Evidence has been accumulating since 1921 to show that there may be two and possibly more hemolytic substances in staphylococcus toxin antigenically distinct from each other.<sup>11,35,60,83</sup> Walbum<sup>96b</sup> noticed a peculiar type of hemolysis which took place in the ice-box after a preliminary period of incubation at 37° C. when goat cells were used. Bigger<sup>5</sup> and his associates at first concluded that the lytic substance responsible for the destruction of sheep cells was different from the rabbit-erythrocytic hemolysin. Furthermore, these two fractions show little or no antigenic activity. Bigger<sup>5</sup> later suggested, however, that the difference in the lysis of sheep and human red cells may be due to several hemolysins present in the filtrate, although such lysis could be explained by the presence of only one hemolysin and other accessory substances that inhibit or aid the hemolysis. Glenn and Stevens<sup>35</sup> found two antigenically separate substances in a single staphylococcus filtrate. They called these hemolysins alpha and beta. The former lysed rabbit and sheep cells at 37° C., the latter hemolyzed only sheep corpuscles when they were placed in the ice-box. Bryce and Rountree<sup>11</sup> confirmed the observation of Glenn and Stevens<sup>35</sup> and reported strains of staphylococci that produced only Beta hemotoxin.

The Alpha hemotoxin is most frequently encountered in staphylococcus filtrates and apparently it is the one from which the international standard unit of antitoxin was prepared. If subsequent investigations substantiate the work of Smith and Price<sup>87</sup> that strains of staphylococci pathogenic for man produce a significant amount of Beta hemotoxin then it may be necessary to change the present standard unit of antitoxin.

The demonstration of two or more hemolytic substances in a staphylococcus filtrate; the limited knowledge which we have at present with regard to the formation of toxin and the mechanism of lysis of red blood cells, all contribute to a greater confusion when the subject of one or more fractions in staphylococcus toxin is discussed. Burnet,<sup>14a</sup> Parish and Clark,<sup>70</sup> Nélis,<sup>63</sup> and others think that staphylococcus toxin contains only one substance that produces lesions in many different tissues. Nélis<sup>63</sup> found that the rate of destruction of the hemolysin by heat paralleled the rate of destruction of the other toxic properties. I have also found that the rate of destruction of the hemolytic fraction parallels the rate of destruction of the skin necrotizing factor.<sup>79j</sup> Burnet<sup>15</sup> observed that all the fractions attributed to staphylococcus toxin were destroyed at a parallel rate by formaldehyde. The skin necrotizing and the hemolytic factor are also destroyed at the same rate when this toxin is shaken with either chloroform or ether. Travassos<sup>92</sup> and others have found that staphylococcus antitoxin neutralizes all the different fractions in staphylococcus toxin.

Other investigators, among whom there are Dolman,<sup>25a</sup> Parish,<sup>70</sup> Panton and Valentine<sup>69</sup> and Forssman<sup>31</sup> think that some of the fractions in staphylococcus toxin may be the same substance but that there are more than one responsible for the diversified effects produced by this toxin. Parish and O'Meara<sup>71</sup> express the opinion that the intradermic value of toxin approximates to the hemolytic value when rabbits' red blood cells are used. Panton and Valentine<sup>69</sup> find that the hemolysin and the dermo-necrotic toxins are closely associated and that there is no relation, however, between these and the leukocidin.



A gastro-intestinal or enterotoxic fraction was attributed to the staphylococcus first by Barber<sup>3</sup> in 1914. This substance has been studied subsequently by Jordan and his associates,<sup>42,43a,b,c</sup> Dolman,<sup>24c,e,26,27</sup> and many others. Staphylococcus filtrates containing this enterotoxic substance may produce vomiting, gastro-enteritis, diarrhea, fever and collapse in the human when taken by mouth.<sup>24c</sup> Some investigators have obtained similar symptoms following the ingestion of the filtrate in experimental animals. The mechanism of the effects produced by this toxin is not known. The pathologic lesions accompanying staphylococcus food poisoning apparently have been studied only in a few cases.<sup>7</sup>

Several controversies have arisen over this enterotoxic substance. Woolpert and Dack,<sup>99</sup> and Dolman<sup>27</sup> and his associates report that it is distinct from the toxic substance frequently produced by the staphylococcus. They contend that it is antigenic and that it is present after heating filtrates for 30 minutes at 100° C. Eaton<sup>28</sup> states that this enterotoxic substance may be a metabolite and not a true toxin. Jordan and Burrows found it non-antigenic and unlike other well-defined toxins; it is soluble in organic solvents.

Davison and Dack<sup>20</sup> attribute the following properties to staphylococcus enterotoxin: "It is relatively heat stable, but prolonged boiling or autoclaving gradually decreases its potency. It is not extracted from filtrates with chloroform. The varying results indicate that some undetermined factor controlled alcoholic precipitation. However, the enterotoxin retains its potency after treatment with alcohol, while the lethal staphylococcus toxin is destroyed. It is salted out of solutions saturated with ammonium sulfate, but not from those half saturated."

It is of interest to note that Woolpert and Dack could demonstrate gastro-intestinal toxin in none of the staphylococcus filtrates without other toxic substances also being present. There seemed to be a rough correlation between the amount of food poisoning substance and the other toxic factors.<sup>99</sup>

All the tests suggested for determining the presence or absence of "food poisoning strains" of staphylococci apparently have proven unsatisfactory. The results of the cultural method described by Stone<sup>88</sup> does not parallel that of Dolman's kitten test.<sup>27</sup> In the latter, young kittens are given an intraperitoneal injection of the filtrate. If they vomit the filtrate contains the enterotoxic factor. I found that kittens and young puppies would vomit following the intraperitoneal injection of infusion broth as well as with staphylococcus toxin.<sup>79b</sup>

There is very little definite information on the mode of action of staphylococcus toxin. Animals given a small amount of a potent toxin intravenously may die in 2 to 5 minutes. At autopsy, no gross lesions are demonstrable. Glynn<sup>36</sup> has found degeneration of the mitochondria in the tubular epithelial cells of the kidney after this short interval. Hemorrhages and capillary dilatation are the characteristic pathologic lesions found when the toxin is given intravenously and a period of only a few hours elapses before death. Focal and diffuse areas of necrosis occur in many of the viscera if the animal survives 15 hours or longer following an intravenous injection of a potent toxic filtrate. In view of these pathologic lesions it would seem that staphylococcus toxin injures directly the cells. There is a variation in the suscepti-

bility of the different cells to this toxin as shown by the difference in the pathologic process in the different viscera. The sudden death which so frequently follows the intravenous injection of staphylococcus toxin may indicate that a large number of cells are severely injured and an insufficient time elapses for these cells to undergo the histologic changes that are recognized as those following a severe injury. Animals that survive the acute effects of staphylococcus toxin die apparently as the result of the action of the toxin on the parenchymatous tissue. Such a form of death is well illustrated by those animals that develop renal necrosis following an intravenous injection. They show a marked retention of non-protein nitrogen in the blood at the time of death.<sup>79m</sup>

**VII. Physiologic Effects of Staphylococcus Toxin.** Some of the physiologic effects produced by staphylococcus toxin have been studied and apparently they are closely associated with certain pathologic lesions previously described. Russ<sup>84</sup> and Kellaway, Burnet and Williams,<sup>47</sup> have observed an immediate drop in blood pressure following the intravenous injection of staphylococcus toxin. Russ thought that this effect was the result of an obstruction in the pulmonary circulation. Kellaway and his co-workers were of a similar opinion. They also thought that there was some pharmacologic substance in the medium which in addition affected the blood pressure. Infusion broth when injected intravenously into anesthetized dogs produced a drop in blood pressure similar to that which occurs when staphylococcus toxin is injected into the same animal. In this experiment I was unable to determine whether or not the drop in blood pressure was due to the staphylococcus toxin or to some other constituent in the filtrate.<sup>79c</sup> In view of the injury to endothelial cells by the toxin it is very likely that there would be a fall in blood pressure following the injection of staphylococcus toxin. Until this toxin is obtained in a chemically pure form it would appear difficult to determine the effect of it on the blood pressure.

Nélis and Bouchaert<sup>64</sup> observed a progressive decline in the blood pressure which was also accompanied by a preliminary slowing of the heart and was followed by the appearance of extrasystoles and finally culminating in ventricular fibrillation. Dingle<sup>23</sup> and his co-workers, in studying the effect of staphylococcus toxin on the rabbit's heart with electrocardiographic tracings observed evidence of severe myocardial damage accompanied by venous engorgement preceding collapse and death. They concluded from their experiments that death resulted from the direct action of staphylococcus toxin on the myocardium.

Nélis and Bonnet<sup>65</sup> have observed the effect of staphylococcus toxin on the central nervous system. The toxin was injected into the cranial cavity and into the spinal canal. The effect is characterized by muscular contractions, convulsive movements, respiratory and cardiac difficulties and death. The rapidity with which death occurs is influenced by the quantity and potency of the toxin. Nélis thinks that staphylococcus toxin affects the respiratory center and that this is the mechanism of its lethal action.

**VIII. A Consideration of the Mode of Action of Staphylococcus Toxin.** The mechanism of the effects produced by staphylococcus toxin is suggested by the pathologic lesions and the physiologic changes observed. The mitochondrial changes described above in the renal tubular epi-

thelium apparently are not the only early acute injuries produced by this toxin. It is very probable that almost every functioning cell in the body is more or less severely damaged by staphylococcus toxin following the intravenous injection of a large dose. The dilated capillaries throughout the body and the presence of small hemorrhages suggest that this toxin injures the capillary endothelium. Blood escapes from the vessels as a result of this capillary damage. Staphylococcus toxin may therefore be considered an endothelial poison.

The cellular lesions which follow the local injection of staphylococcus toxin resemble those which occur in some of the viscera following an intravenous injection of the same filtrate. Coagulation of the cytoplasm in many of the cells throughout the body suggests that staphylococcus toxin may unite very readily with certain tissues. As a result of this union the cells are either partially or completely destroyed.

Levine,<sup>52</sup> considering the mechanism of the effects of the hemolytic fractions in staphylococcus toxin, concludes from his experimental studies that the so-called "hot-cold lysis" is not a special case, due either to "abnormal toxins" or to an interfering substance. It may be only an expression of the same basic principle which controls adsorption in general.

The rate of union of toxin with red cells may be influenced by the composition of the toxin as well as that of the cell. Seiffert<sup>55</sup> has shown that staphylococcus toxin is not fixed by the hemoglobin but by certain substances in the red cell, probably a lipid or combination of lipoids. The formation of some substance by this lipid and toxin alters the permeability of the cells and allows the escape of hemoglobin.

There are many observations to show that staphylococcus antitoxin given before a lethal dose of staphylococci or staphylococcus toxin inhibits death. This apparently would support the idea that toxin unites with cells to produce its injurious effect.

A single toxin may injure many different types of tissue. The degree of injury may be influenced by the type of cell as well as the concentration of toxin in the cell. In view of the effects of staphylococcus toxin on different tissues and the lack of experimental data to disprove it, there appears to be sufficient evidence to assume that staphylococcus toxin has at least one substance that lyses red blood cells, necrotizes the skin, destroys leukocytes, produces necrosis in the kidney and causes acute death of animals.

**IX. Immunity.** Staphylococcus antitoxin has been recognized since Van de Velde,<sup>93</sup> in 1894, described it along with his observations on leukocidin. This antitoxin is frequently found normally in the serum of humans and experimental animals. Bryce and Burnet<sup>10</sup> have studied the antitoxic content of the serum from individuals from birth to the seventh decade. They found that natural immunity is present at birth, presumably the result of a passive transfer from the mother. This antitoxic immunity is lost during the first few weeks of postnatal life. It slowly develops again during the first year and reaches the adult level at approximately the sixth year and remains more or less constant until old age, at which time a slight fall occurs.

The antitoxic content of sera found in adults may have resulted from unrecognized antigenic stimuli. There is a variation in the titer from

different individuals. The antitoxic content of sera can usually be increased by a series of injections of staphylococcus toxin, toxoid or by prolonged infection with certain staphylococci.<sup>8,13a-d,25b,30,97</sup> Animals with an increase in the antitoxic titer exhibit an increased skin resistance to the necrotizing effect of staphylococcus toxin, according to Dolman and Kitchings.<sup>25b</sup> There is no definite parallelism, however, between the increase in the amount of circulating antitoxin and the degree of acquired skin resistance to toxin.

Natural antistaphylococcal immunity occurs in the rat and in the wild rabbit similar to that in the human.<sup>10</sup> There is some evidence which indicates that this immunity in the rat may be actively acquired through a series of infections.

Rats born from mothers immunized either during gestation or a very short time before pregnancy have a sufficient number of antibodies after 30 days to survive a lethal dose of staphylococcus toxin given intraperitoneally. In the study of this immunity it has been impossible to determine whether or not the antibodies passed directly from the mother to the fetus through the placenta or if the antigen passes the placenta and the antibodies are produced by the fetus.<sup>79h</sup>

The method of increasing the antitoxic titer by a series of injections of staphylococcus toxoid has offered an apparently satisfactory way to treat many of the clinical cases of skin infections due to the staphylococcus.<sup>24b,77</sup> This form of therapy, however, has not given satisfactory results in the treatment of osteomyelitis.<sup>8,12</sup>

Another method of immunization was possible when experiments showed the antitoxic titer of serum could be increased by a series of injections of either staphylococcus toxin or toxoid. The antitoxin thus formed neutralizes staphylococcus toxin both *in vivo* and *in vitro*.<sup>24d,45,67,70,77,79h,89</sup> Pröschner,<sup>76</sup> in 1903, stated that "the first stipulation which we request for an antistaphylococcus serum which would have therapeutic value for man is that such would protect experimental animals against staphylococcus infections. This postulate has, up to now, not been filled." At present there is considerable experimental data to show that staphylococcus antitoxin given to rabbits will protect them against a lethal dose of a broth culture of staphylococci. This antitoxin also protects rabbits against the toxin derived from several different strains of staphylococci.<sup>67</sup>

Recently, in studying the effect of staphylococcus antitoxin on the reaction produced by toxin and non-toxin producing strains of staphylococci, it was found that mice previously passively immunized showed a marked increase over the untreated controls in the number of neutrophils and the degree of phagocytosis of the bacteria.<sup>79c</sup> The lesions produced by the toxin were also inhibited in the immune mice. These experimental results confirm the opinion expressed in 1936 by Ramon and his associates.<sup>78</sup> They stated that the antitoxin protected the cells and tissues against the necrotizing action of staphylococcus poison and thus made a less favorable medium for the growth and multiplication of the organism.

Smith,<sup>86b</sup> in studying the relationship between circulating antitoxin and resistance to experimental infection with the staphylococcus, found that the resistance of rabbits to the intravenous injection of strain

Wood 46 is correlated with the alpha antitoxin content of the serum. Antitoxin, however, does not prevent the development of localized staphylococcus lesions when the organisms are given intravenously. Mercier's<sup>58</sup> observations indicate that staphylococcus antitoxin may prevent lesions produced by the local inoculation of staphylococci.

The inhibitory effect of staphylococcus antitoxin on staphylococcus toxin may be shown *in vitro*. Antitoxin is added to blood agar at the time the medium is poured into petri dishes. Staphylococcus toxin, when dropped on the surface of blood agar, causes a zone of hemolysis to form; however, this lysis does not occur when the medium contains specific amounts of the antitoxin. Furthermore, hemolytic strains of staphylococci, when grown on the surface of blood agar media containing antitoxin, shows either an absence or inhibition of the hemolytic zone about the colonies.<sup>79a</sup> Sulfapyridine added to blood agar media inhibits the rate of growth of the colonies; however, it does not have any effect on the toxin produced by the staphylococcus.<sup>80</sup> Experiments now in progress show that sulfapyridine when given intravenously to rabbits does not prevent death produced by an intravenous injection of staphylococcus toxin.

Smith<sup>86a</sup> has presented some of the problems that may be encountered in the testing of antigens for comparative potency. She has also called attention to the inhibitory action of glycerol on the necrosis produced by staphylococcus toxin in the skin of the rabbit and the guinea pig. The action of glycerol, sucrose and glucose in inhibiting the necrosis is one of partial destruction of the toxin, according to Smith.<sup>86c</sup> I have observed a similar inhibitory effect produced by hypertonic solutions of sodium chloride on rabbits' red blood cells and also upon the skin necrosis produced by this toxin. When staphylococcus toxin is added to red blood cells in hypertonic sodium chloride solutions the degree and rate of lysis is inhibited. Apparently some change occurs in the red blood cell to render it refractive to the hemolytic action of staphylococcus toxin. Sodium chloride, added directly to staphylococcus toxin in a quantity sufficient to make a 12% concentration, does not destroy the hemolytic action.<sup>79o</sup> Rabbits injected intradermally with hypertonic solutions of sodium chloride and the bleb subsequently injected with toxin fail to show necrosis at the point of injection, but skin necrosis does occur below this site. The inhibitory action of sodium chloride on the dermal necrosis may be the result of the action of the salt on the tissue cells. The change effected may inhibit the union of the toxin and the cells. Staphylococcus toxin apparently is not neutralized by sodium chloride in the tissue since necrosis frequently occurs inferior to the point of injection of the toxin in areas previously treated with a hypertonic concentration of sodium chloride.<sup>79b</sup>

The experimental results in the treatment of staphylococcus infection would indicate two approaches to clinical therapy: first, an attempt to neutralize the toxin and, second, to increase phagocytosis of the bacteria. The choice of therapy in any case must be influenced by whether or not the staphylococcus produces a toxin. If the organism produced no toxin, then any method by which the number of phagocytes can be increased apparently is indicated. If the bacterium produces a potent toxin then an increase in the antitoxic titer is of prime importance. It

neutralizes the toxin before further tissue damage occurs. In any staphylococcus infection, immunity will be aided if the organism can be rendered more susceptible to phagocytosis either by increasing the opsonin or the agglutinins. The experimental results in a study on passive antitoxic immunity indicate that an increase in the number of leukocytes and an increase of phagocytosis occurs when the animal is given staphylococcus antitoxin.

Holman's<sup>39</sup> statement made in 1935 is still significant. "The progress during the last few years has greatly increased the knowledge of the mode of infection and wide potential powers of the staphylococci, and there is hope that more scientific methods of treatment and prevention may develop if all the various aspects of the problem can be properly correlated and effectively evaluated."

**X. Miscellaneous.** The standard unit of staphylococcus antitoxin was accepted by the League of Nations, Bureau of Biological Standards in 1935. It contains 0.0009502 gm. of standard staphylococcus antitoxin and is based on the hemolytic, skin-necrotizing and lethal factors in the toxin. These units have been accepted by the National Institute of Health and are as follows:

The hemolytic unit of toxin (H. U.) is the smallest amount of toxin which causes complete hemolysis (4+) of 1 cc. of a 1 % saline suspension of fresh washed rabbit red blood cells.

The hemolytic test dose (L. H.) is that quantity of staphylococcus toxin which is just neutralized by 1 unit of United States Standard Antitoxin as is evidenced by inhibition of hemolysis.

The dermonecrotic dose (R. D.) is the smallest amount of toxin which causes necrosis in an area 0.5 cm. in diameter when injected intradermally into the skin of a healthy albino rabbit.

The dermonecrotic test dose (L. R.) is that quantity of toxin which is just neutralized by 1 unit of United States Standard antitoxin, as manifested by inhibition of dermonecrosis.

The minimum lethal dose (M. L. D.) is the smallest amount of toxin which causes the death of a healthy white mouse weighing between 17 and 22 gm.

The lethal test dose (L+) is that quantity of toxin which is just neutralized by 1 unit of United States Standard staphylococcus antitoxin, as manifest in the survival of the test animal (white mice).

Since this article on Staphylococcus Toxin was accepted for publication, Dr. J. E. Blair has published an interesting review article on "The Pathogenic Staphylococci" (*Bacteriol. Rev.*, 3, 97, 1939).

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## PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

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### EPIDEMIOLOGICAL ASPECTS OF MOTTLED ENAMEL.

MOTTLED enamel is a characteristic abnormality of the teeth, caused by the ingestion of excessive amounts of fluorides. It ranks well up among the commoner dental anomalies, both in the extent of its distribution through the world, and in the number of persons it affects. The disease is of unusual public health interest because prevention is the only known method for its control. Once established, the condition persists throughout life because treatment is limited to efforts at cosmetic improvement, and natural recovery does not take place.

The results that have been attained in the study of mottled enamel during the past few years, serve as an excellent illustration of what can be accomplished through application of epidemiologic methods to the study of a non-communicable disease. As a matter of fact, a number of specialists in the field of public health have found an interest in mottled enamel. To the nutritionist the disease is unusual in that it is caused by an excess of the causative agent, rather than the deficiency with which he is so frequently concerned. The water-works engineer



encounters a disturbing situation, in that his traditional and ever present source of safe water, the deep well, too often gives rise to this disease through an excess of fluorides. To the dentist, the condition is unique in that it is the only well established anomaly which is sharply limited to endemic zones or geographic regions. The chemist has found an incompletely answered problem in attempting to develop simple, accurate methods for the quantitative determination of fluorine in food substances, and for the economical removal of fluorides from potable water.

**Relation of Mottled Enamel to Other Forms of Poisoning by Fluorine.** Distinguished from the several forms of chronic fluorosis—which include mottled enamel—are the occasional instances of acute poisoning. The most obvious lesions come from corrosive action on the mucous membranes, and on the skin. The clinical manifestations are in direct contrast with those of chronic fluorine intoxication, where systemic effects are absent unless the dosage is relatively large and long continued; and where the changes that follow are the result of selective localization of the chemical in tissues.

Roholm<sup>47</sup> summarized the literature of acute fluorine poisoning from 1873 to 1935, recording 60 fatal and 52 non-fatal cases. The most common sources were insecticides, rat poisons, and disinfectants. The clinical manifestations were those of acute gastro-enteritis, convulsions and paresis, with terminal vasomotor collapse. From animal experiments<sup>49</sup> and from observation of humans<sup>48</sup> a single dose of fluoride below the level at which toxic symptoms develop, has been shown to cause changes in the calcifying tooth characteristic of mottled enamel, although limited of course to a relatively small part.

Other pathologic and physiologic changes besides mottled enamel are known to result from chronic fluorosis. A characteristic sclerotic affection of the bones, which sometimes extends to adjacent structures, occurs in workers engaged in the cryolite industry<sup>39,47</sup> through exposure to dust containing fluorides. Bishop<sup>8</sup> reported similar bony changes in an industrial worker exposed for 18 years to rock phosphate dust. Shortt *et al.*<sup>53</sup> reported 10 adult patients with advanced fluorosis, where symptoms first appeared at about 30 years of age. Smith<sup>56</sup> was unable to find any bony changes in children with marked mottled enamel and felt that the teeth were much more sensitive to fluorine than the bony skeleton.

Rather recently interest has been given to a possible interrelationship between the metabolism of fluorine and thyroid activity.<sup>26</sup> Apparently fluorine can be stored<sup>43b</sup> in the thyroid in relatively high concentrations, although most of the evidence points against any direct relation between fluoride ingestion and actual enlargement.<sup>26</sup>

Despite the general assumption that defective teeth predispose to dental caries, McKay<sup>36c,36d</sup> long ago stated, that although representing the most poorly constructed enamel of which there is any record in dentistry, the teeth of mottled enamel show no greater liability to dental caries than do normally calcified teeth. Epidemiologic contributions of a number of workers<sup>2,32</sup> from several countries<sup>4,25</sup> have strongly indicated that the ingestion of fluoride bearing waters is associated with a decrease in the incidence of dental caries. That the active

principle is fluorine, has not been satisfactorily established. Other evidence,<sup>38</sup> while confirming the phenomenon, suggests that no greater importance can be attached to the fluoride content of drinking water than to its total hardness. It is possible that a wholly independent constituent is the answer. If fluorides do act as a protective factor in dental caries, that action is independent of the presence of mottled enamel, as indicated by the field studies thus far made in America.<sup>14e,19</sup> These investigations have been limited to children less than 16 years old, and have been principally concerned with regions where the usual concentration of fluoride in water is relatively low, although sufficient to cause mottled enamel. This associated interest in studies of mottled enamel is now attracting much interest.

The effects that follow ingestion of fluorine depend upon the dose, the mode of entry into the body, the duration of exposure, the type of fluorine compounds, the age of the individual, the composition of the diet and other less well understood factors. Until more is learned about these variables, and until the conditions that govern the secondary manifestations of chronic fluorosis can be determined, an understanding of mottled enamel would seem to rest on the premise that the calcifying tooth is more sensitive to the action of fluorine than are other tissues of the body, and that the milder forms of mottled enamel occur without other manifestations of chronic fluorosis.

**Definition of Mottled Enamel.** This hypoplastic abnormality of the teeth results from taking excessive amounts of compounds of fluorine into the body during that period of childhood when calcification of the enamel is under way. Under such circumstances, both dentin and the enamel of teeth are imperfectly formed.<sup>7</sup> When the tooth erupts, the enamel is abnormally opaque and chalky white, in contrast to the pearly, translucent appearance of normal enamel. White blotchy areas are usually interspersed with the areas of more or less normal enamel, a situation which has led to the very descriptive term of mottling.<sup>9</sup> Because this dental condition is the result of fluorine intoxication, usually over a long period of time, and because of its occurrence in localized geographical regions, the name "chronic endemic dental fluorosis"<sup>14d</sup> has recently been introduced.

This dental defect was first called *Denti di Chiaie*, having been recognized in Italy well in advance of 1901.<sup>23</sup> In Argentina it is known as *dientes veteados*. *Darmous*, a dental and mandibular disease among herbivora and man in certain parts of North Africa; and *gaddur*, a dental and bone disease among herbivora in Iceland occurring after volcanic eruptions, are undoubtedly more extreme forms of chronic fluorine intoxication, of which mottled enamel is only a part of the clinical reaction.

Since many health officers and practicing physicians have not had opportunity to become as familiar with mottled enamel as have dentists, consideration is next given to its clinical nature. There follows an account of the various etiologic factors. Principal emphasis is given to epidemiologic studies in the field, which have better defined the problem and as so frequently happens, have formed the basis for improved administrative practice for its control.

**Clinical Recognition.** When exposure to fluorides has been essentially continuous since birth, the condition of mottled enamel becomes clinically evident as soon as the permanent teeth have erupted. The cause lies in the action of fluorine at the time the enamel is in the process of calcification and hence takes place in the pre-eruptive stage of tooth development. Affected teeth are ill formed, rather brittle, dull and chalky white.

A definite relation exists between the amount of fluoride ingested, the fluorine content of the tooth, and the extent of clinical damage. When exposure has been great, the affected enamel tends soon after eruption to become pitted or even corroded. As a rule the pits and corroded areas are more pronounced on the labial surfaces and may be completely absent lingually. The pitting and corrosion are the macroscopic reflection of fracture of smaller or larger groups of enamel rods. When the exposure to fluorine has been both severe and continuous the tooth appears uniformly chalky instead of mottled.

A characteristic discoloration of the teeth is an added feature of more severe intoxications. This may range from light yellow to brown and even to black, and is commonly referred to as brown stain. It is never present when the tooth erupts and only appears in enamel already mottled. In contrast to other types of dental staining, it is located within the enamel structure, rather than on the surface. A most peculiar feature is the regularity with which it is confined to the outer surfaces of the upper front teeth,<sup>36</sup> the lower incisors being spared. The disfigurement may be extreme.

Under exceptional circumstances, eruption of the teeth may be delayed, they may then be abnormally small, and may erupt in abnormal positions with resulting malocclusion.<sup>28</sup>

Because the permanent teeth calcify at different times and over a period of many years, and because calcification of the crown of any single tooth requires from 4 to 6 years, it is evident that with varying degrees and periods of exposure to fluorides, the extent and degree of mottling may vary, not only in different teeth but in parts of the same tooth. The ultimate effect from chronic fluorosis can only be determined years after the damage has been done. On the other hand, although ingestion of fluorides after the crown of the tooth has formed will sometimes result in a deposition of fluorine, especially in the pulp and dentin, it will not cause the changes in tooth structure characteristic of mottled enamel.

An accepted scheme for grading degrees of clinical reaction is essential for epidemiologic studies, and is often useful in clinical and public health practice. It must take into account the numbers of teeth affected, clinical severity as indicated by pitting and corrosion, and the presence and intensity of the stain. The simple but inclusive arrangement of Dean<sup>14b</sup> and his co-workers<sup>17</sup> is followed to good advantage in community surveys. Details are to be found in the original papers. The excellent illustrations of Dean, McKay and Elvove<sup>20</sup> and of Roholm<sup>47</sup> aid materially in the interpretation of the classification.

**Experimental Production of Mottled Enamel.** The first significant contribution toward determining the direct cause of mottled enamel was that by McCollum, Simmonds, Becker, and Bunting in 1925.<sup>35</sup>

Knowing that normal teeth frequently contain fluorine, they proceeded to determine experimentally the effect on tooth development of an excess of this element. When sodium fluoride was added to a normal diet of rats, in amounts but little more than many foods contain, marked abnormalities of the teeth constantly occurred. Although the lesions were similar to those of mottled enamel in man, described by Black and McKay<sup>9</sup> 9 years previously; no one associated the two conditions. Bergara<sup>6</sup> later described a symmetrical dark stain in the teeth of white rats, occurring 4 months after first receiving a diet containing sodium fluoride. Tolle and Maynard<sup>60</sup> confirmed the work of previous investigators, by feeding rats sodium fluoride. Continuing their experiments they used rock phosphate and triple superphosphate—both of which contain fluorine—in place of sodium fluoride. The changes that followed were the same. Chaneles<sup>11</sup> reported on the histopathology of the teeth of animals fed sodium fluoride.

These studies established that a characteristic abnormality of teeth could be produced by ingestion of fluorides. A possible connection with mottled enamel of man was not considered. Proof that the experimental and the naturally occurring disease were of similar nature and uniform cause, came from epidemiologic investigations in the field.

**Epidemiological Contributions to Etiology.** The first observations antedate experimental production of the disease by many years. Kühns,<sup>30</sup> in 1888, described anomalies of the teeth that are identifiable as mottled enamel. A family had returned to Germany from the town of Durango in Mexico. Those members of the family who had been born in Mexico had irremovable black spots in their teeth. He felt that the color of the teeth was possibly due to the presence of oxides of manganese resulting from the action of the sun on manganese salts deposited in the teeth from drinking water. Eager,<sup>23</sup> an officer of the United States Public Health Service, stationed in Naples, Italy, published in 1901 an account of his observations on defective enamel of the teeth among Italian emigrants, particularly those coming from Pozzuoli, a community near Naples. It was a matter of common belief, locally, that the condition was in some way concerned with the water supply and with volcanic emanations.

That the disease existed in America, first became generally known in 1902,<sup>37</sup> when practicing dentists in Colorado Springs undertook a systematic investigation. Beginning in 1906, Black<sup>9</sup> carried on extensive and fundamental studies of the disease over a period of 10 years, much of the work being in collaboration with McKay. A series of papers,<sup>9,37</sup> published in 1916, gave the name of mottled enamel to the condition and accurately described the endemicity and time factors involved. They presented supportive evidence to show that it was caused by certain water supplies. Subsequently McKay<sup>36a</sup> extended these observations to show close association with artesian waters. While thus relating the cause of the disease to common water supplies, they had no idea of the specific factor involved.

In 1925 McKay<sup>36b</sup> made a survey of Oakley, Idaho, in the course of which he found that the children of the town who used the municipal water supply regularly developed mottled enamel. Children from several families who used a nearby spring water were not affected. On

his recommendation, the latter supply was substituted as the source of drinking water for the town; this being the first instance of a community changing its water supply for the sole purpose of preventing mottled enamel.

A survey of Bauxite, Arkansas, made by Kempf and McKay<sup>29</sup> in February, 1928, might be termed the classical field study of this condition. Bauxite was a town established in 1901 to provide homes for the employees of a mining company. The original domestic water supply came from shallow surface wells and a few springs. As the population increased, a larger supply was required, and in 1909 a well was drilled to the depth of 255 feet, later augmented by two other deep wells. Most of the shallow wells were gradually filled in, and for the community proper the deep wells were the principal sources of supply. The 1928 survey included complete histories and dental examinations of 458 school children. From these data it was learned that no case of enamel defect antedated the introduction of the deep-well water. The oldest individual affected was born about the time that it was introduced. All persons in the community, who had used the deep-well water during any considerable period of enamel formation, exhibited the defect. Certain individuals, although residents of the community and attending school there, lived beyond the distribution of the deep-well water and depended upon the original shallow wells. They had normal enamel. Other environmental factors, and the mode of life and dietary habits of the people, were much the same in the village and outside the village. There was no differentiation by economic class. The use of water from the central deep wells during the time of enamel formation, seemed to be the single common factor. Persons intermittently exposed had mottling only of teeth in the process of enamel formation at the time of exposure. Other teeth were essentially normal. The extraction of a temporary molar from the mouth of a native Bauxite child showed the underlying bicuspid to be typically mottled, prior to exposure to mouth conditions. As a result of this survey the deep wells were abandoned. The new water supply was drawn from the Saline River, a source also used by the neighboring town of Benton where children showed no evidence of mottled enamel. Ten years after this change was made, a second study of Bauxite by Dean, McKay and Elvove<sup>20</sup> showed that mottled enamel among children of the community had ceased then just as suddenly as it had started when the deep-well supply was introduced.

Two separate lines of investigation had led to the situation in 1930 where a striking abnormality of teeth had been produced experimentally in the rat by feeding fluorides; and where a well established dental anomaly of humans had been related to water supplies. The two observations remained uncorrelated.

The many epidemiologic investigations had naturally led to detailed analyses of water supplies associated with mottled enamel, but examination for fluorides had been omitted. Influenced by the qualitative demonstration of fluorides in deep-well waters from Bauxite, Arkansas—these tests were made by Petry, but never reported—Churchill<sup>12</sup> extended the observation to waters from Oakley, Idaho, Colorado Springs, Col., and other towns where mottled enamel was known to be present. He found fluoride in all samples examined. He noted also that waters

containing appreciable amounts of fluoride tended to occur in certain geographic regions, but that mottled enamel was not present in all cities consuming fluoride bearing waters. His methods of analysis lacked sufficient quantitative accuracy to permit conclusion that the cause of mottled enamel was due to the ingestion of fluorides, but he suggested further investigations with this in mind. The work of Smith, Lantz, and Smith<sup>58</sup> definitely established the point in 1931.

Mottled enamel was prevalent in St. David, Arizona. From observations in that locality, Smith and her co-workers<sup>58</sup> first showed that the water supply contained from 3.8 to 7.1 parts per million of fluorine. They next proved experimentally that the lesions associated with chronic fluorosis in the white rat were identical with those of mottled enamel in man. Similar dental defects were produced in rats by feeding them sodium fluoride, and by giving them concentrated St. David water. A quantitative relation was found to exist between the amount of fluoride ingested and the presence of lesions. The amount required for development of the experimental disease in rats was greater than that which produced mottled enamel in humans. The explanation lies in the difference in rate of growth of the teeth, and also explains why animals are usually not involved in regions where humans regularly develop mottled enamel. These observations were promptly substantiated by Velu<sup>61b</sup> with proof that a similar ailment in North Africa, called *darmous*, was also chronic fluorosis.

Sebrell, Dean, Elvove, and Breaux<sup>52</sup> investigated the water of Conway, South Carolina. It contained 6 parts per million of fluorine, and had produced typical mottled enamel in humans. When concentrated by methods similar to those of Smith, Lantz, and Smith,<sup>58</sup> and fed to rats, it produced typical dental defects. They then made a synthetic drinking water, comparable to the concentrated natural Conway water and containing all of the ions present in amounts greater than one-half part per million, with the single exception of fluorine. This water produced no noticeable abnormality in the teeth of white rats. About the same time, McKay<sup>36c</sup> made a second survey of Oakley, Idaho, to determine the effect of changing from a water supply that contained fluorides to one that did not. Further development of mottled enamel had not occurred.

**Pathogenesis.** The gross and microscopic pathology of mottled enamel has been well described, but the manner in which fluorine causes these changes is still controversial. Fluorine is usually absorbed from the gastro-intestinal tract, very uncommonly from the lungs.<sup>47</sup> Surprisingly little is known of the form in which it is absorbed, circulated, stored, or excreted. As a general principle, fluorine is rather efficiently absorbed and but slowly excreted. Furthermore, it would seem that fluorine in low concentrations may have a stimulating effect, and in high concentrations be inhibitive to normal function of the invaded tissue. The concentrations giving rise to these paradoxical effects likewise vary with different animals, and for different tissues of the same animal. Some evidence has been presented to show that administration of relatively large amounts of fluoride causes a negative calcium balance,<sup>34,47</sup> inhibits certain enzyme systems,<sup>21</sup> affects the parathyroid glands,<sup>13,46</sup> and exhibits a special relation to vitamin C metabolism.<sup>41,42,44</sup>

Evidences of abnormal calcium-phosphorus metabolism and the other effects mentioned, have been demonstrated, however, only at intake levels much higher than is necessary to cause mottled enamel.

Most theories proposed in explanation of the mode of action of fluorine have been based on the assumption that fluorine in some way causes its adverse effects by direct toxic action on the enamel-forming tissue. A close correlation exists, however, between the fluorine content of enamel and the severity of mottling,<sup>3,10,33</sup> regardless of the particular tooth, or the animal under consideration. Although all of the manifestations of fluorine storage and fluorine intoxication cannot be explained on a pure physico-chemical basis, there is a striking similarity between the behavior of fluorine in nature and its behavior in animals. In nature it is commonly found in combination with calcium (fluorspar), and with tricalcium phosphate (natural rock phosphate). Neither compound is very soluble in water, but natural rock phosphate is much less so than calcium fluoride. Several groups of workers<sup>1,5,24b,31</sup> have demonstrated that calcium fluoride in water is effectively and rapidly removed—to a certain minimal level—by tricalcium phosphate. In fact, this compound is one of the best agents for removing fluorides from potable waters. Since calcium phosphate, together with calcium carbonate, is the essential component of enamel and of bone, it is not surprising that Smith and Smith<sup>64</sup> obtained good results by using ground bone for the same purpose. In animals and man, the best evidence indicates<sup>46</sup> that fluorine occurs in the teeth and in the bones as a fluorapatite-like compound not greatly dissimilar to that found in nature as natural rock phosphate. There is considerable evidence, then, of a physico-chemical affinity between fluorine—especially calcium fluoride—and calcium phosphate, and that this affinity manifests itself both in nature and in the living organism.

A clearer idea of the mechanism by which the condition of mottled enamel is established in man, can perhaps be obtained by considering the kinds of change possible in bone generally, when exposed to fluorides. A more or less constant metabolic process takes place in bone,<sup>51</sup> with an interchange of components. Thus, sufficient amounts of the tricalcium phosphate component are free to act at any time, with formation of a fluorapatite-like substance. With very small amounts of fluorine entering the circulation, the changes that follow can be conceived as being of such slight moment that no demonstrable lesions become evident, and the process is comparable to simple storage. With larger amounts, the substitution would be sufficient to produce excessive amounts of abnormal fluorine-containing bone, an increase in the size of the bone and a pathologic condition called by Roholm<sup>47</sup> osteosclerosis. At very high levels of fluorine absorption,<sup>47</sup> as in gaddur, there is a toxic inhibitory effect on bone itself, associated with manifest generalized toxic symptoms. Presumably low grade metabolic changes in the bony substance would continue even when appreciable amounts of fluorapatite were present. If exposure to fluorides ceased, or continued only in slight degree, normal rather than fluorine-containing bone would tend to be reformed. This is consistent with observed recession of abnormal bony changes when exposure to fluorides ended.

The enamel of teeth, however, is not subject to this constant meta-

bolic interchange of chemical constituents. Calcium phosphate and other elements which go to make up the enamel are free to combine with such unusual substances as fluorine, only when the enamel is being formed. Thereafter, enamel behaves like a dead tissue, whether it is normal or abnormal.

It does not seem physiologically sound furthermore, to postulate that larger dosage is required to injure a rapidly growing tissue, than one growing slowly—the explanation commonly given for the larger amounts of fluorine needed to produce the disease in the rat compared with man. Explanation of the phenomenon would seem to rest equally well on a purely physical basis. With more newly formed enamel in a given time, more fluorine would be required to produce an equal effect. This is offered as a more reasonable explanation than the theoretically enhanced toxic action on young growing tissues.

**Sources of Fluorine in Nature.** Fluorine has been estimated<sup>64</sup> as thirteenth in order of importance among the elements composing the earth's crust, thus placing it ahead of any of the other halogens and far ahead of such toxic elements as lead, arsenic and mercury. As industry has advanced, the use of fluorine compounds has progressively increased. Industrial development in turn was one of the important factors leading to an increased urban population, the greater need for community water supplies, and consequently the greater use of deep-well waters. In the United States the development of the west resulted in a shift of population to regions now known to be fluoride areas. In all of these ways, the potential exposure to fluorine compounds increased.

The recognized importance of fluoride bearing waters in chronic endemic dental fluorosis, and the relative ease with which the element can be determined in water, are the principal reasons for the major attention this source of fluorine has received. The widespread distribution of compounds of fluorine in nature requires consideration of other sources—in food, in association with industry, from medicinal substances, and in some localities, contact with volcanic dusts.

A number of reasons exist why more attention has not been given to these other potential sources of fluorine. The causal relationship to mottled enamel was only established in 1931. The possibility of other health aspects has been recognized still more recently. Accurate quantitative methods had to be perfected for examining the diverse materials concerned. That primary attention was given to endemic areas where whole populations were affected, is also understandable. The situation is in many ways comparable to the evolution of our attitude toward typhoid fever. To date we have been attracted by epidemics, as was Budd in his early studies of that disease. As epidemics become less frequent, attention must shift to sporadic cases, to mild and low grade affections, and perhaps even to the prototype of subclinical infection in typhoid. This will require better understanding of the effects from low concentrations of fluoride in water, less than that required for manifest endemic prevalence. When chronic fluorosis of water-borne origin is eliminated, a residual incidence may well remain as it has in typhoid; and again as in typhoid, attributable to sources distinct from those concerned with dramatic outbreaks.

Chronic endemic dental fluorosis is associated with water supplies



which contain 1 part per million or more of fluorides.<sup>15,57b</sup> The content of fluorine in a given water supply is influenced by geological conditions. Judgment should accordingly be based on the average of a number of examinations over a period of months. Supplies containing 1 to 4 parts per million are frequent in certain areas and some with as much as 20 parts per million have been reported in the United States.<sup>24a</sup> Mottled enamel can occur, however, when the water supply contains less than 1 part per million, although usually less than 10% of children in the community are affected and these in mild degree. Deep well and artesian waters more commonly contain fluorides in amounts dangerous to health than do surface waters, although much depends on the geological formation of the particular region.<sup>40</sup>

Few foods are wholly free from fluorine. The fluorine associated with plant products may be a constituent of the food itself, be admixed, or deposited on the food. That within the plant itself can be derived from the soil, the fertilizer used, or the irrigation water. External contamination comes from dusts and sprays. The great variation in conditions under which food is produced, as well as the varying capacity of plants to take up fluorine from the soil, suggests essential differences in the fluoride content of plant foods. A monograph by McClure,<sup>33</sup> just recently available, summarizes a series of studies on the fluorine content of foods. Values for plant foods are expressed on the basis of dry substance; animal, fish and other substances on the basis of the food as consumed. Beans, wheat, oats, rye and corn commonly contain 1 to 3 parts per million. Wheat in a certain fluorite area contained 226 parts per million. Green vegetables such as beans, broccoli, celery, cabbage, lettuce and spinach, and such fruits as apples, may have higher amounts of fluorine than the seeds, especially if the plants are sprayed. Roots and tubers, such as turnips, carrots, potatoes and peanuts, usually have less than 1 part per million.

Meat products usually contain much less fluorine than might be expected; on the basis of the fluorine content of water and plants consumed by the animals from which they are derived. The selective storage in bone spares those parts most frequently used as food. Nearly all salt water fish contains appreciable amounts, varying from 1.5 parts per million in oysters to as high as 12.5 parts per million in canned salmon. Fresh water fish contains no more fluorine than meat.

Exposure to dusts containing large amounts of fluorides is an important factor in certain parts of Africa,<sup>28</sup> but not in the United States. Sources of exposure in industry have little relation to mottled enamel, because of the peculiar conditions that essentially restrict development of the disease to childhood. No case of mottled enamel has been attributed to medicines or disinfecting agents, probably because they are used for relatively short periods. Nursing mothers exposed to fluorine in industry<sup>47</sup> have apparently transmitted the condition to their infants.

Not much is known of the epidemiologic significance of sources other than water. As independent factors in causing classical mottled enamel, they probably are not important. They may well supplement the fluorides derived from water, where the level is borderline, to such an extent as to be the determining factor. The place of fluoride containing foods will be better appreciated as more is learned about what follows

long continued ingestion of minimal and subtoxic amounts of fluorine. Probably a good deal depends on individual variations in intake and in food habits. Given comparable conditions of dosage and time, experimental evidence would indicate that foods containing fluoride are as active<sup>33</sup> in producing mottled enamel, as are waters.

**Prevalence.** An extensive study of the distribution of mottled enamel in the United States was made by Dean<sup>14a</sup> in 1933. From the literature, by questionnaires to dental societies and individual dentists, and by field studies, he found 97 areas where mottled enamel was definitely a problem, 98 in which it probably existed and 5 others for which data were incomplete. Later information<sup>16</sup> indicated about 375 known affected localities distributed through 26 states. The general area most affected in this country is the Southwest, including the states of Texas, New Mexico, and Arizona.<sup>55</sup> The largest concentration of affected communities is in the panhandle-west Texas region.<sup>17</sup> A second general region is south of the Great Lakes, from Ohio<sup>50</sup> to the Dakotas.<sup>18</sup> These three states, on the basis of present information,<sup>40</sup> have more affected communities than intervening jurisdictions such as Wisconsin,<sup>22</sup> and Illinois,<sup>56</sup> but the condition is well recognized in all of the area. The disease is known to occur in several of the Rocky Mountain and Pacific Coast states, and a limited focus has been determined in Virginia and the Carolinas. Of the usual groupings of states, all have been concerned except the New England and Middle Atlantic regions. The actual distribution by states and the relative frequency of the condition can only be approximated, because some state health departments have done little or no survey work.

Mottled enamel is by no means a problem confined to this country. Its world distribution is substantiated by recent reports from Canada,<sup>62</sup> China,<sup>63</sup> Japan,<sup>59</sup> and India<sup>45</sup> among others. The general world prevalence as determined by Dean,<sup>14d</sup> McKay,<sup>36f</sup> and Roholm,<sup>47</sup> shows that mottled enamel in the Americas occurs not only in the United States and in Canada, but also in Mexico, Argentina, Barbados and the Bahama Islands. The disease has been infrequently identified in Europe but is known to be present in Italy, Spain, England and probably Holland. In Africa the condition is widespread in Algeria, Tunisia and Morocco where there are large phosphorite deposits. It is also known in the Sinai peninsula and in certain parts of South Africa, as well as in the Azores and the Cape Verde Islands. In Asia the affection has been reported from several places in North China and Japan. Australia is the only continent where mottled enamel has not been found. As the clinical nature and epidemiologic relations of mottled enamel become better appreciated, present information will likely be found to represent but a fractional part of the actual distribution.

A naturally acquired disease of domestic animals, analogous to mottled enamel in man, was first reported by Velu<sup>61a</sup> in his studies of *darmous* in North Africa. Dean<sup>14c</sup> found a somewhat similar condition among dairy cattle in Horry County, So. Carolina. Because of these observations, the experiments of Phillips, Hart, and Bohstedt<sup>43a</sup> have special interest. Even when cows were fed fluorides in sufficient amounts to produce toxic symptoms, there was very slight excretion in the milk. Furthermore, storage of fluorine in muscle is slight.<sup>33</sup>

The cow would seem to be of little importance as an intermediate source of fluorine, either through milk or meat.

**Age Incidence.** Susceptibility to mottled enamel is limited to a sharply defined age group. The reason is that fluorine can be deposited in enamel only during the time that the crowns of the permanent teeth are calcifying. This period is from infancy, when the central incisors may be affected, until 16 years of age when calcification of the crowns of the last teeth, the third molars, has been completed.<sup>20</sup> A further characteristic of the disease is the long lag between the time when the actual damage is done and the time that it becomes objectively apparent, corresponding to the interval between completion of calcification and actual eruption of the tooth. Because the various teeth calcify at different periods, intermittent or interrupted deposition of fluoride affects only certain teeth. Dean cites illustrative experiences where older high school children were observed with all teeth normal except the third molars, these being persons who had taken up residence in the endemic area when 8 to 10 years of age. By contrast, high school students in other localities have had all permanent teeth severely affected except the third molars, which corresponded with the time a change was made to a satisfactory water supply. Such examples are unusually significant in determining the part of water supply in production of the disease, for the element of individual susceptibility is eliminated. The frequency of the disease bears no relation to color or sex<sup>14d</sup> nor are weather and latitude of moment.

Mottling of the enamel of temporary teeth is very uncommon. This is explained by the fact that for these teeth enamel formation is practically completed by the time of birth, and that the placenta has a protective influence.<sup>27</sup> The principal food of the infant, milk, contains only slight amounts of fluorine.<sup>43a</sup> Furthermore, the rate of development of the deciduous teeth is faster than that of the permanent teeth,<sup>48</sup> and it is known that the faster a tooth develops the higher is the concentration of fluorine necessary to cause mottled enamel. Under special conditions these protective factors may not be sufficient to prevent mottling.<sup>29,53,57a</sup>

Mottled enamel cannot develop in persons exposed after the sixteenth year of life. However, the dentin may be adversely affected, resulting in general weakening of the tooth structure.<sup>56</sup> The impression exists,<sup>14d,47</sup> unsupported by satisfactory evidence, that adults exposed to relatively large amounts of fluoride have an increased incidence of gingivitis. Teeth of adults unaffected by mottled enamel have been repeatedly shown to contain fluorine. Roholm<sup>47</sup> also believes that adult teeth subjected to fluorine have an increased growth of both cement and dentin, and a consequent narrowing of the pulp cavity. Other possible effects of chronic fluorosis in adults, such as changes in bone and action on the thyroid, have already been mentioned.

**Methods for Field Surveys.** Mottled enamel has been shown to be of sufficiently wide distribution that most individual health officers will want to know to what extent the problem is a matter of concern in their immediate jurisdictions.

The first thing to do is to look at a map. The geographic areas involved have been fairly well defined. Chemical examination of the

community water supply will demonstrate whether or not fluorides are present in sufficient amounts to constitute a potential hazard. On the basis of that information a few hours spent with dentists of the community will soon determine whether dental conditions corresponding to mottled enamel are occurring in the permanent teeth of children, and how long that situation has existed. This information will determine the need for a field survey. An adequate sample of school children is selected, of ages ranging from 6 to 16 years. Individual histories are obtained in respect to principal and secondary water supplies that have been used—how constantly and for how long. The information is confirmed by interviews with the parents. The most important part of the survey is a satisfactory dental examination by a practitioner familiar with the disease. The results of individual examinations are interpreted according to the scheme proposed by Dean, Dixon, and Cohen,<sup>17</sup> from which is determined the mottled enamel index. This is an arbitrary measure of the extent and severity of mottled enamel in a community. If less than 10% of the sample of children examined show mottled enamel, the index is considered negative. A negative index is sometimes mistakenly interpreted as meaning that the community is free from mottled enamel. This is not necessarily true. It simply means that the condition is not prevalent in endemic proportions. The 6 positive gradations expressed by the index, ranging from borderline to very marked, are based on a combination of numbers of persons affected—always more than 10%—and the general severity of the disease. The determination of any 1 of these 6 situations shows the need for active preventive measures.

**Control of Mottled Enamel.** Prevention is the only method of control, since very little can be accomplished by treatment of the disease once it has developed. In the light of much experience, McKay<sup>36/</sup> states that cavity margins can only be established with difficulty because of the chalky texture of the teeth. Stains near the surface may be remedied by grinding off the surface of the tooth, down to normal enamel. A porcelain jacket crown is frequently applied for cosmetic reasons. When mottled enamel occurs with the average level of severity that has been noted in Arizona,<sup>56</sup> the cost of adequate dental care to the individual up to adulthood is about a thousand dollars, at which time the natural teeth must frequently be replaced with artificial dentures.

Considering the disfiguring effect of mottled enamel, that it is not subject to improvement by natural process or medical treatment, that every child born and reared in an endemic area is almost certain to have the condition in some degree, it is evident that chronic endemic dental fluorosis is a problem worthy of serious attention. As with most situations in preventive medicine, there is no single ideal program for control, practicable under all circumstances.

The most obvious thing to do is to get a water supply having a content of fluorides within safe limits. Depending on local conditions, sources of fluorine other than water may have to be given consideration. Attention to certain features of hygiene and of the general environment can be helpful.

With respect to the water supply, the most economical procedure in the long run, is to provide a new source of supply. The convincing

results obtained by Oakley, Idaho,<sup>36</sup> Bauxite, Arkansas,<sup>20</sup> and Andover, So. Dakota, are sufficient to prove that this measure is completely satisfactory.<sup>16</sup> If the existing supply contains unusually large amounts of fluoride, it is about the only thing to do, because of the difficulties and cost of purification. The choice of the new supply depends upon local geologic conditions. In Illinois,<sup>65</sup> for example, surface waters are almost always low in fluorides, and can be readily substituted for supplies drawn from deep wells. Occasionally a rather sharply defined offending geologic stratum can be avoided<sup>65</sup> by staying above it or by going deeper and easing it off.

Providing the fluoride content of the existing supply is not excessive, an alternative procedure is to dilute the water with that from a second source essentially free from fluorides, thereby bringing the final content of fluorine below 1 part per million. The method is to be considered, when available surface supplies are alone insufficient to meet the requirements of the community. Such supplementary supplies can be obtained from shallow wells, small lakes, gravel packed wells in creek bottoms, or similar sources.

In a considerable number of small areas, and in at least one large region of the United States, the panhandle of Texas, there are few adequate fluoride-free sources of supply. The water must then be treated. This is usually an expensive procedure if all the water used in the community is processed. Treatment can be limited to that used for cooking and drinking, but with the objections that always attend dual water supplies. Of the many processes proposed,<sup>40</sup> the lime method<sup>60</sup> appears to be the most economical when it can be used. Treatment with triecalcium phosphate<sup>5</sup> is rapid, cheap and effective, but has not yet had sufficient field tests to fully establish its usefulness. Mechanical agitation of water with an added chemical such as magnesium oxide,<sup>24b</sup> and subsequent settling, has the disadvantage of being a slow process and requiring more attention than do filtration methods.

Food is the other principal consideration; just how important, remains to be determined. That some foods demand more attention than others has been demonstrated. The prohibition of fluoride sprays for vegetables and fruits is a means of protection. Fluoride compounds should not be used as a preservative of foods. The use of steam pressure cookers as a substitute for the boiling of vegetables is not known to have been previously suggested, but appears wholly logical in regions where fluoride bearing waters are common. By this method vegetables are cooked in a suspended container, and concentration of fluorides in the prepared food is avoided.

A well balanced diet will not prevent mottled enamel.<sup>66</sup> Avoiding a deficiency of vitamins C and D and of calcium is to be recommended, if for no other reason than to prevent the independent damage such deficiencies may cause in teeth. More milk and less water in the diets of children serves to decrease total intake of the element. In certain parts of Africa and South America protection must be afforded against dusts containing fluorides, a hazard not present in other countries.

**Summary.** Mottled enamel is a hypoplastic dental abnormality, caused by ingestion of fluoride compounds at any age between infancy and 16 years. The number of teeth involved depends upon the time

and duration of the exposure. The severity of mottling depends upon the amount of fluorine taken into the body during the period of calcification of the enamel. The disease primarily affects the permanent and not the deciduous teeth. Once developed, the condition is permanent. Water supplies are the principal source of the causative agent, but others, such as foods, must be considered. All of the things that give rise to mottled enamel enter into the life of people of all ages. Therefore, a program for control must be conceived on a community basis.

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## PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF JANUARY 16, 1940.

The Study of Reproduction in Rats on Purified Diets. CLAIRE FOSTER, DORIS RUSSELL and J. H. JONES (Departments of Pediatrics and Physiological Chemistry, University of Pennsylvania, and the Children's Hospital of Philadelphia.)

A Study of Isolated Muscle Fibers From a Protoplasmic Standpoint. L. V. HEILBRUNN (Department of Zoölogy, University of Pennsylvania). The protoplasm of muscle cells resembles the protoplasm of various other types of cells in being peculiarly sensitive to the calcium ion. If an isolated frog muscle fiber is immersed in isotonic calcium chloride solution, the ends immediately become plugged. This is a reaction presumably identical with the surface precipitation reaction as studied in marine egg cells and in protozoa. As the calcium entering the ends of the fiber comes into contact with more and more of the protoplasm, the fiber becomes transformed into plug material and shortens until it is only about one-fourth of its original length.

When isolated muscle cells are placed in solutions which tend to rob them of calcium ion, they become insensitive to electric condenser discharges. Their irritability is regained on return to solutions containing calcium.

These facts are interpreted in terms of the calcium release theory of stimulation.

The Influence of Cutaneous Atmospheric Oxygen Absorption Upon the Apparent Total Oxygen Utilization of the Body. ALFRED H. CHAM-

BERS and SAMUEL GOLDSCHMIDT (Laboratory of Physiology, University of Pennsylvania). Respiratory oxygen exchange was determined by the Tissot method on subjects enclosed up to the neck in a metal box. The gaseous atmosphere surrounding the body could be changed at will.

Two of four subjects increased their oxygen consumption from the inspired atmospheric air up to 10%, or more, when moist nitrogen replaced the room air surrounding the body. In the other two subjects the rise, under similar experimental conditions, was either entirely absent, upon occasion, or, at other times, increased to a slight degree.

The results can be explained on the assumption that the oxygen for cutaneous metabolism is partially, at least, derived from the surrounding air. When deprived of the atmospheric source, an increased utilization from the blood is demonstrable. The oxygen which penetrates the skin may be used entirely by the cutaneous cells or, when its tension is high, it may gain entrance into the blood of the skin; at other times it is possible that, because of a higher tension of oxygen in cutaneous blood due to increased skin circulation, little is utilized from the atmosphere.

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**The Rôle of the Hypothalamus in Cardiovascular Regulation.** R. F. PITTS, M. G. LARRABEE, D. W. BRONK, and F. H. LEWY (Eldridge Reeves Johnson Foundation, University of Pennsylvania). In order to evaluate the rôle of the hypothalamus in cardiovascular regulation, we have compared the character of the spontaneous activity in peripheral sympathetic nerves, as well as its reflex modification, before and after extirpation of the hypothalamus. In addition, we have studied the activity induced in these nerves by stimulation of the hypothalamus. In these latter experiments stimulating electrodes were oriented in the supra-optic and tuberal portions of the hypothalamus by means of the Horsley-Clark stereotaxic instrument, and brief repetitive condenser discharges delivered at controlled intensities and frequencies.

The characteristic grouping of spontaneous activity in the various fibers of the sympathetic nerve trunks and their reflex inhibition and excitation were in no wise altered by extirpation of the hypothalamus.

Stimulation of the hypothalamus at frequencies above 10 per second produced an increase in sympathetic activity in the inferior cardiac and cervical sympathetic nerves, and after a brief latency a rise in blood pressure. Frequencies from 1 to 10 per second often produced an inhibition of sympathetic activity and a fall in blood pressure. Records from few fiber preparations indicated that the individual units discharged more frequently and that more units were brought into activity as either stimulus frequency or intensity were increased.

It has been possible to record from single fibers of the cervical sympathetic activated from the hypothalamus. Frequency of discharge was greatest at the beginning of stimulation, but after a period of a second or so, a steady state was attained and the unit discharged rhythmically, the frequency of discharge being directly related to the intensity and frequency of hypothalamic stimulation.



There is, following stimulation of the hypothalamus, an abrupt inhibition of all spontaneous sympathetic activity and a reduced excitability of the lower sympathetic centers to either reflex excitation from afferent nerves or to hypothalamic stimulation.

These experiments show how the chemical and reflex control of sympathetic centers are modified by varying degrees of hypothalamic activity.

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THE  
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ORIGINAL ARTICLES.

LIFE EXPECTANCY AND MORTALITY FROM SKIN AND LIP  
CANCER.\*

BY SIGISMUND PELLER, M.D.,

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SOMETIMES a cured skin cancer patient develops another cancer to which he succumbs. Is the risk of such a discouraging metachronous combination of a surface and an internal cancer great?

According to Dublin and Lotka,<sup>1</sup> cancer shortens the life of the average person at 42 years by 5.2%, at 52 years by 6.2%, and at 62 by 6.8%. The shortening of life for the cancer victims themselves, is, of course, greater. The life shortening effect of cancer depends upon the site and the cellular type of the malignancy. Most of the surface cancers are relatively benign. However, as some of these patients die of the disease, this disease is bound to shorten the life even if it is not, or only very seldom, followed by an internal cancer.

In order to estimate the life shortening rôle of the skin and lip cancer one can depend less on the causes than on the frequency of death and on the time elapsed since the onset of the illness.

In this paper such an attempt has been made. I have studied 715 cases, from the histories of the lip and cheek epithelioma patients at the Kelly Hospital between 1921 and 1931 and the eyelid cases for the years 1921 to February, 1929. All cases were included, whether treated or not. Where the time of onset of the cancer was unknown, the age at the first entrance to the hospital was taken as onset. If a lesion had been persistent for a long time without signs of progress, the dates of previous surgical or Roentgen ray treatments were regarded as onset. In the case of metachronous epitheliomas, the first epithelioma was chosen as significant.

\* This work was done while the author was a guest investigator in the Department of Biology of the School of Hygiene and Public Health of The Johns Hopkins University, using the records of the Kelly Hospital, Baltimore. For the results or conclusions reported the author is solely and entirely responsible.

**Age Distribution.** The average age of 695 patients with given age data at the onset of the disease was  $58.6 \pm 0.3$  years. This is 11.1 years less than the average age at death from skin and lip cancer, as reported in the official statistics of the United States (69.7 years). In our material, the ratio of lip cancer (307 out of 715 cases) is much higher than in the official mortality statistics. The lip cancer patients were at the onset (2.5 years) as well as at the time of death (1.5 years) younger than the skin cancer cases. The real difference between the onset of the surface cancer and the death is, therefore, a little smaller than 11.1 years.

According to hospital records, patients suffering from internal or breast cancer are also much younger than one would expect on the basis of the mortality statistics. The reason for this is the selection of cases which undergo surgical treatment. However, such a selectional factor is not involved in the case of surface cancers admitted to a hospital known for its non-surgical methods.

TABLE 1.—AGE DISTRIBUTION OF FACE AND LIP CANCER PATIENTS OF BOTH SEXES.

Age.	Kelly Hospital, Baltimore.				U. S. Registration Area, 1930-1933.	
	Age at:				Age at death from cancer of:	
	Onset of disease.		Death.		Skin.	Lip.
	Absolute frequency.	Percentage frequency.	Absolute frequency.	Percentage frequency.	Percentage frequency.	Percentage frequency.
29 . . . . .	9	1.3	..	..	1.8	0.6
30-39 . . . . .	51	7.4	1	0.6	2.3	2.4
40-49 . . . . .	105	15.1	6	3.6	5.5	6.6
50-59 . . . . .	180	25.9	26	15.5	11.3	14.1
60-69 . . . . .	192	27.6	41	24.4	19.3	24.8
70-79 . . . . .	130	18.7	58*	34.5	30.5	31.2
80+ . . . . .	28	4.0	36*	21.4	28.9	20.2
? . . . .	20	..	1	..		
	715	100.0	169†	100.0	100.0	100.0

\* Including 1 death after closed period of observation.

† Including 2 deaths after closed period of observation.

Generally, it is believed that persons suffering from skin or lip cancer are older than other cancer patients. This holds true for the age at death. Considering, however, that on the average the duration of surface cancer is much longer than that of an internal malignant tumor, one has to realize that at the onset of the illness there is practically no difference in age between sufferers from a skin or lip cancer and the total of all other carriers of a malignancy.

**Mortality.** During the first 5 years after the onset of the illness, there occurred 78 deaths; in the second quinquennium, 53 deaths; in the third, 29; and still later, 9 deaths. In order to evaluate these figures, they were related with the total number of years of the respective age group. Patients change in due time the age group to which they belong. Therefore, person-years instead of cases were counted and each one of the years which elapsed since the onset of the illness was placed in the respective age group.

Altogether the material collected covers 4860 person-years; 2603 of them belong to the first quinquennium after the onset of the epithelioma; 1462 to the second; and finally 795 person-years where the onset of the illness was at least 10 years earlier. The percentage of deaths rises with the number of years passed since the appearance of the tumor. In the first quinquennium, 3 deaths; in the second, 3.7; and in the further 5-year periods 4.9 deaths correspond with 100 person-years. By eliminating the different age distribution the differences in the death rates diminish, the standardized rates being 3.0, 3.3, and 3.8 respectively. The basis for these calculations is the age at the onset of the disease. In 295 of the 695 patients the onset was considerably beyond the time of the first attendance. Therefore, only 400 patients are an unselected unit. Among the 295 patients, however, there were some with a definite turn to the unfavorable course of the disease or even in a hopeless condition before their very first visit to the Kelly Hospital. The real death rates of an unselected material should therefore be lower, than indicated in our figures. On the other side, the 295 patients were at their first attendance at the Kelly Hospital survivors of other contingents of patients, with whom they shared an average of 3.2 years. Probably, during these 3.2 years of the cohort to which they belonged formerly a number of patients died. Applying the general mortality rates to these 295 patients one may assume that they should be complemented by 31 deaths, 24 of which should have occurred during the first quinquennium of the disease. Thus the standardized death rate of the first 5-year-period will increase to 3.9, of the second to 3.5 and of the later periods to 4.2%.

The number of actual deaths differs from that expected according to the U. S. Life Tables which were used in this paper as a basis for all calculations.

TABLE 2.—DEATH RATES PER 100 PERSON-YEARS IN FIRST AND ALL SUCCEEDING 5-YEAR-PERIODS AFTER ONSET OF DISEASE, KELLY HOSPITAL.  
PERSONS WITH FACE AND/OR LIP CANCER.

Age at time of observation.	First quinquennium.			All following quinquennia.			Death-rate for all years.	U. S. Life Table, 1929-1931; death-rate, 100qx.*
	Person-years.	Deaths.	Death-rate.	Person-years.	Deaths.	Death-rate.		
39 . . .	174	1	0.6	43	..	..	0.46	0.43
40-49 . . .	409	3	0.7	268	3	1.1	0.89	0.81
50-54 . . .	304	5	1.7	240	6	2.5	2.10	1.30
55-59 . . .	377	10	2.7	279	5	1.8	2.30	1.90
60-64 . . .	371	8	2.2	362	9	2.5	2.30	2.75
65-69 . . .	360	13	3.6	353	11	3.1	3.40	4.10
70-74 . . .	286	12	4.2	323	17	5.2	4.80	6.25
75-79 . . .	169	10	5.9	225	19†	8.4	7.40	9.40
80- . . .	122	15	12.3	134	21†	15.7	14.00	16.00
? . . .	31	1	3.2	28	..	..	1.70	
	2603	78	3.0	2257	91‡	4.1	3.50	3.90

\* The symbol 100qx denotes the chance for 100 persons, at the age x, of dying within 1 year, namely between the ages x and (x + 1).

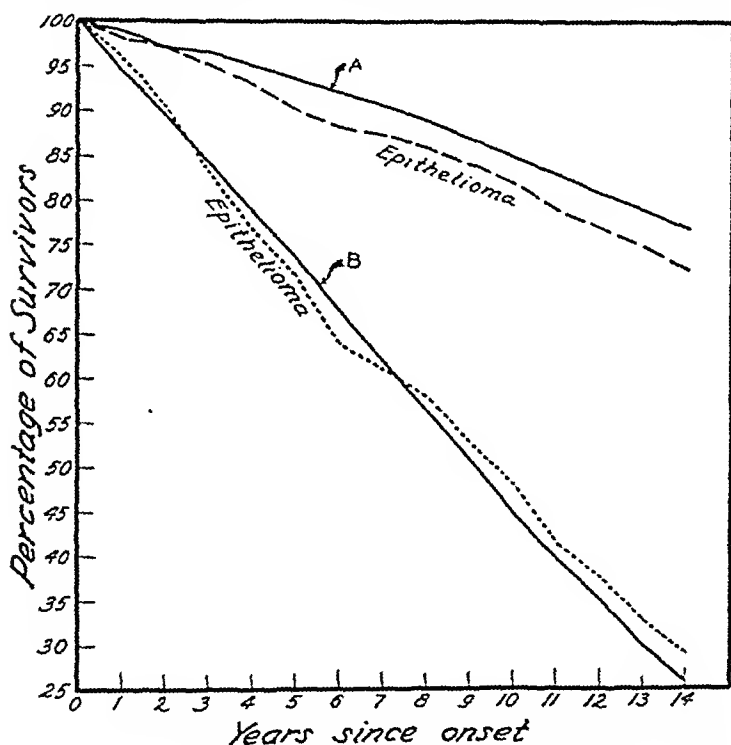
† Including 1 death after closed period of observation.

‡ Including 2 deaths after closed period of observation.

In the ages below 60 there are more, and in the higher age groups fewer deaths than would be expected from the general life-table.

Of all patients with given age 168 died, whereas 191.8 deaths would be expected (30.8 deaths before, and 158.7 after the first attendance at the Kelly Hospital). In the age groups below 60 years, 33 deaths were registered and only 26 ( $=7 + 19$ ) calculated, the respective figures for the higher ages being 135 and 163.5 ( $=23.8 + 139.7$ ).

Assuming, in conformity with Welch and Nathanson,<sup>2</sup> that the mortality of cases lost is about as that of the group which remained under care, I calculated mortality and survival rates for each successive year after the onset of the disease. From the fourth year on, patients at the age of 21 to 59 have lower survival rates than the average (curve *A*), whereas persons with onset of the epithelioma at the age above 59, after 7 years of the illness have passed, show higher survival rates than the general population (curve *B*).



GRAPH 1.—CURVE OF SURVIVORS OF 726 PATIENTS SUFFERING FROM SKIN OR LIP EPITHELIOMA.

**Expectation of Life.** If the 695 skin and lip cancer patients were a random sample of the general population, then they should expect to live, according to their age distribution at the onset of their illness, another 11,626 years. (By using life tables for the Maryland population, the life expectation would have been smaller than here.) That makes an average of 16.7 years per person. Of the 11,626 years only 4800, *i. e.*, 40% were covered by observation, counting the time from the onset of the illness up to the death (one group), or up to the time of our investigation (second group), or up to the date

of disappearance (third group of patients), respectively. The younger the patients, the smaller the part of the life expectation which could be tested by observation.

TABLE 3.—EXPECTATION OF LIFE AT ONSET OF THE FACE AND LIP EPITHELIOMA AND THE NUMBER OF YEARS TESTED SINCE THEN. (KELLY HOSPITAL.)

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Age at onset.	No. of patients.	Expected years		Patients who							Years which remain to be covered.
		$\bar{e}_x^*$		Died.			Did not die.				
				Lived since onset.						All.	
				Total.	Av.	No.	Yrs.	Av.	No.		
21-39 . .	60	2045	34.1	6	50	8.3	54	442	8.1	492	1553
40-49 . .	105	2690	25.6	16	142	8.8	89	843	9.5	985	1705
50-59 . .	180	3353	18.7	31	189	6.4	149	1206	8.1	1404	1949
60-69 . .	192	2400	12.5	58	396	6.8	134	837	6.2	1233	1167
70-74 . .	77	677	8.8	24†	120	5.0	53	243	4.6	363	314
75+ . .	81	462	5.7	33†	157	4.8	48	166	3.5	323	139
	695	11,626	16.7	168	1063	6.3	527	3737	7.1	4800	6825
*											

\*  $\bar{e}_x$  is the symbol for the expectation of life at the age x, called also mean after-life-time at that age. Calculation made on basis of U. S. Life Table, 1929-1931.

† Including 1 who died a few months after closed period of observation.

In order to fulfill the normal life expectancy of the 695 patients the 527 persons still living at the end of the observation period (Column 8, Table 3) would have to live another 6825 years (Column 12). A random sample of 527 individuals of the given age distribution has a life expectancy of 7135 years. However, among these 527 cases there were 14 with recurrent epithelioma (according to the age: 3+1+5+3+1+1) and 46 with uncured glandular metastases or already in a hopeless condition or persons with a primary cancer of an internal organ (8+7+7+12+9+3). For the sake of argument, I abandoned entirely these 60 cases, counting them all *a fond perdu*, as if they all had died on the first day after the end of the observation period. At this day the normal  $\bar{e}_x$  of the 60 cases would have been 1043 years, thus leaving for the remaining 468 cases an  $\bar{e}_x$  of 7135-1043 = 6092 years. Considering that 6825 years had to be covered, a deficit of 734 years remains. That is about 6% of the total number of years the 695 patients (Table 3, Column 2), had had to live at the onset of the disease.

Depending on the age, the deficit is larger or smaller. Of the persons who developed an epithelioma at the age of 20 to 49 years, at the end of our observation 115 were free of symptoms and other 9 persons still ill but without any complications (as metastases, recurrent epitheliomas or primary internal tumors). The  $\bar{e}_x$  of these 124 persons at that time was 2666 years, whereas 3258 still had to be covered. Thus the 165 persons with an onset of the illness between 20 and 49 years of age will probably have a final deficit of  $\frac{592 \times 100}{4735} = 12.5\%$  of their life expectancy as indicated in Column 3 of the last table. The higher the age at which the epithelioma

first appeared, the lower this final deficit. Cases with onset of the disease at 50 to 59 probably will fall short only 4.0% of the normal life expectancy, and in those of the age group 60 to 69 the final deficit will apparently not exceed 3.2%. Patients who developed their first epithelioma at an age above 70 seem to live at least as long and probably longer than the average of persons of the same age. Excluding from the 101 persons still alive (Column 8, ages above 70) those with a recurrent epithelioma or with metastatic affections and with an internal cancer, we got 73 persons free of symptoms and 15 still uncured but without any complications. The further life expectancy of these 88 persons was  $438 + 92 = 530$ , whereas only 453 years (Column 12) had to be covered. It is a surplus of  $\frac{77 \times 100}{1139} = 6.8\%$ .

**Life Expectancy of Cases Which Were at Least 6 Months Under Observation.** A considerable number of the patients recorded in the former tables were only for a very short time under observation. The endeavors of the Kelly Hospital to follow them up were fruitless. By omitting all who were lost after less than half a year, except those who died during this time, the total number of cases (of known age) shrinks to 547. On the average the fatal cases lived 6.3 years, and the non-fatal cases 9.3 years from the onset of the disease (Columns 5 and 8, Table 4). Of the total life expectancy (Column 3) 4577 years, *i. e.*, 48.6% are covered by observation. This percentage depends on the age of the patient, rising from 36 in the youngest age group to 75% in the age group above 70 years.

Excluding from all further calculations 39 persons suffering from a recurrent\* or metastatic epithelioma or from an internal malignancy,† there remain 340 persons (317 free of symptoms, and 23 still ill) with a further life expectancy (according to the U. S. Life Tables) of 4324 years, while 490 more would be necessary in order to cover the total  $\sum_x$  of the 547 cases at the onset. The final deficit is, thus, 5.2%.

In general, Table 4 confirms the former results. Patients suffering from an epithelioma at ages below 49 have a larger deficit (about 10%) than those whose first epithelioma develops at 50 to 69 years of age (4 and 3% respectively); whereas patients with onset above 70 most probably will live longer than the average population. Of the 57 persons still alive at the end of our observation period, 47 were free of symptoms and 3 still ill but without any complications. These 50 persons had a further life expectancy of  $271 + 17 = 288$  years while only 204 years remained to be covered. Neglecting entirely the further life of the complicated cases we realize for the entire group of patients over 70 a life surplus of probable  $\frac{84 \times 100}{815} = 10.3\%$ . One will, of course, remember that 208 of the 547

\*  $3 + 4 + 2 + 2 = 11$  cases.

†  $9 + 5 + 9 + 5 = 28$  cases.

patients do not show any mortality during the 731 years of illness in the pre-Kelly Hospital period, while according to the Life Tables 23.2 persons would have to succumb to one of the many causes of death, either cancer or not. Of the 23.2 persons, 10.4 were to be placed in the age group above 70, and added to the 114 patients (Column 2, Table 4). This, however, does not turn the positive life balance of the group into a negative one.

TABLE 4.—LIFE BALANCE OF PATIENTS WHO EITHER DIED OR WERE AT LEAST FOR SIX MONTHS UNDER CARE AT THE KELLY HOSPITAL.

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
Age at onset of disease.	No. of cases.	Expected years of life, $\bar{e}_x^*$	Patients who				All.		Years which remain to be covered.	
			Died.		Did not die.		All.		Total.	
					Lived since onset.					
			Per- sons.	Years. av.	Per- sons.	Years.	Av.	Years.		% of expect- ation.
20-49 . .	139	3980	22	8.7	117	1233	10.5	1425	2555	64.1
50-59 . .	148	2772	31	6.4	117	1162	9.9	1360	1412	51.8
60-69 . .	146	1824	58	6.8	88	781	8.9	1181	643	34.9
70+ . .	114	815	57	4.9	57	334	5.9	611	204	25.0
	547	9390	168	6.3	379	3510	9.3	4577	4814	51.4

\* See footnote to Table 3.

**The Mortality of Persons Successfully Followed Up.** Up to the death or the time of inquiry, 427 persons of known age were traced. Their pre-Kelly Hospital period of illness covered an average of 1.1 years per case.\* After they attended the hospital, the 261 persons still alive lived 2736 years (an average of 10.5 years each), whereas the 168 fatal cases lived 851 years (an average of 5.1 years each). Taking only the time after the Kelly Hospital had been attended, there would be expected for the 20 to 59 year-old patients 19.6 deaths and for the higher age groups 138.1. There occurred, however, 33 and 135 deaths.

TABLE 5.—FACE AND LIP CANCER PATIENTS FOLLOWED UP SUCCESSFULLY. MORTALITY AT THE TIME AFTER THE FIRST ATTENDANCE TO THE KELLY HOSPITAL.

1.	2.	3.	4.	5.	6.
Age.	Persons at the age of attendance.	Years observed at the age.	Life table, 100q <sub>x</sub> *.	Number of deaths.	
				Expected.	Actual.
				At the age of Column 1.	
20-39 . . . .	30	104	0.43	0.46	1
40-49 . . . .	62	436	0.89	3.90	6
50-59 . . . .	118	898	1.73	15.20	26
60-69 . . . .	121	1132	3.58	40.25	41
70-79 . . . .	74	786	7.51	59.00	58†
80+ . . . .	22	223	17.30	38.60	36†
	427	3586		157.60	168‡

\* See footnote to Table 2.

† Including 1 death after closed period of observation.

‡ Including 2 deaths after closed period of observation.

**Life Duration of the Prospective Skin and Lip Cancer Patients.** At any chosen age any population may be divided into  $a$ , persons

\* Living cases 1 and dead cases 1.2 years; patients who could not be traced had a pre-Kelly Hospital period of 1.7 years on the average.



already suffering from cancer; *b*, persons who in the future will develop a surface cancer; *c*, persons who in the future will develop an internal malignancy; and, *d*, individuals who never will produce a cancer. Let us now consider the situation at the age of 40 for persons who in the future will develop a surface cancer. Have they a shorter life expectancy ( $e_0$ ) than an average person at that age?

The answer is: no. On the contrary, they have a higher mean after-life-time than the average population. Persons who later on develop a skin or lip cancer have, of course, by definition a long precancerous period without any deaths. This period lasts from 40 to 60.8 years of age (according to the material of the Kelly Hospital). In the general population of all who lived at 40 years, 24% die during these 21 years. The question to be answered is, therefore, whether the gain of life in the precancerous period is counterbalanced by the excess mortality after the onset of the surface cancer. The answer is again: no. Of all patients above 40 years of age, the life had been checked for 6.9 years on the average. During this time 29%\* of the patients died, whereas on the basis of the life table only 21% is expected. The excess mortality eliminated thus a great part of those who were "supernumerary" at the beginning of the cancer period. After the closed period of observation 71% of all patients were still alive and, on the average, 67.7 years old. The total normal  $e_0$  being 29.7 years, the persons still living would have to live another  $\frac{2 \times 100}{71} = 2.8$  years in order to fulfill the total mean after-life-time. During this time 12% would normally die, and further  $\frac{16 \times 100}{71} = 22.5\%$  would have to die in order to counterbalance the gain of life in the precancerous period (40 to 60.8 years of age). That is improbable.

On account of the death-free period by definition, it may be argued that a comparison of the life expectancy of *future* epithelioma patients at the age of 40 (or 50, 60, and so on) with the average population is methodologically dubious. However, no objection can be made to a comparison between persons who in the *future* will suffer either from a surface epithelioma or from an internal cancer. The death-free precancerous period is common to them and about of the same length. Different in this case is the duration of life after the onset of the disease.

In the United States during 1935 men at ages above 40 who died from causes other than cancer were on the average 70.5 years old. The corresponding figures for men who died of cancer of skin or lip were 70.9, and for all men who died of an internal cancer 65.4 years only. In spite of the gain in life during the precancerous period,

\* Here are also included the probable deaths calculated for the pre-Kelly Hospital period.

the victims of an internal malignancy lost 5.1 years of life, whereas the victims of a surface cancer continued to live after having fulfilled the average life expectation. As a large part of skin and lip cancer patients do not succumb to cancer, the real difference in the age at death between those who developed a skin or lip cancer and the other two groups of the population is greater than 0.4 and 5.5 years respectively. Including women into calculation the differences in favor of the carriers of a surface malignancy become conspicuously larger, the mean age at death for all over 40 being 63.3 (internal cancer), 69.4 (causes other than cancer), and 71.8 years (victims of skin and lip cancer).

**Discussion.** Possibly the material analyzed in this paper is not a fair representation of the average surface cancer patients in the population. A representative material, such as that of the Radium Hemmet in Stockholm, shows more persons freed of symptoms (70% of all skin and 62% of all lip cancer cases; 59% in all of our surface cancer cases), less cancer deaths and death candidates (5%, against 8 in our material) and it shows also a little higher percentage of non-cancerous deaths (17%, against 14.5% in our study). In the material of the Kelly Hospital advanced and complicated cases are apparently more frequent, especially in the younger age groups. Still less favorable are the figures for lip cancer reported by Welch and Nathanson.<sup>2\*</sup>

According to the reports obtained, among the 715 patients of the Kelly Hospital there are 12 who after the epithelioma developed an internal primary tumor. One cannot rely upon these diagnoses. Some of these tumors were rather metastatic, some more likely synchronous. Only a small part of them died in a hospital. In 5 of these cases death occurred at over 70 years. The youngest victim died at the age of 51; the cause of death was a cancer of the stomach and the patient died 2 years after the surface epithelioma appeared. It was, therefore, rather a case of synchronous than of metachronous multiplicity of tumors. In any case, as far as these data indicate, in our study the high mortality of patients at 20 to 59 is not due to a high incidence of second primary tumors in inner organs; it is rather due to a selection of complicated cases.

**Summary and Conclusions.** At the onset of the disease, carriers of an epithelioma of skin or lip are about as old as the average of all other cancer patients. At the time of death cases of skin and lip cancer are older.

The influence upon the life expectation and mortality depends on the age at onset. Skin and lip cancer cases below 60 years have in our material an increased mortality and a shortened life expectancy, as compared with the average population at the same age.

\* Their material was collected in the Pondville and Huntington Hospital, Massachusetts. Only epidermoid and adenocarcinoma cases were considered, the basal cell cancer cases omitted.

Cases with onset of the epithelioma at ages above 70 have a lower mortality and a higher life expectancy.

At the beginning of the "cancer age," at 40 the total group of future carriers of a surface cancer have most probably a future life surplus, compared with the total population of the same age. This indicates that the primary internal cancers developing in those who already have or have had surface cancer are not frequent enough to diminish the life expectancy in this group or to frustrate the value of therapy of the surface malignancies.

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### SCLEREDEMA ADULTORUM.

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THE syndrome which Buschke<sup>1</sup> described at the beginning of the century under the designation "scleredema adultorum" has been accorded scant attention in the American literature. Particularly since the report by Epstein<sup>2</sup> 7 years ago, dermatologists have been alert to recognize the characteristics of scleredema, but internists apparently have not been adequately aware of this distinctive although rare disease. Unfamiliarity has at times promoted confusion of scleredema with the grossly similar entity, scleroderma—an error which carries with it serious prognostic implications. There have been cases in which scleredema not infrequently has been mistakenly diagnosed as acute edematous scleroderma, and the subsequent favorable course has led to unwarranted conclusions regarding the benign nature of certain instances of "scleroderma." Because the onset of scleredema is associated generally with an acute infection, because the outlook for recovery of the patient is excellent, and because the internist is usually the first and sometimes the only medical attendant in such a case, we believe that a general account of this disease might be of interest to physicians other than dermatologists. The pertinent literature has been reviewed in recent contributions by Touraine, Golé and Soulignac,<sup>19</sup> and Sweitzer and Laymon.<sup>18</sup> In this paper we shall present a compilation of the clinical and pathologic features of scleredema as the disease has been observed by us at The Mayo Clinic.

**Material.** The material reported on herein represents a group of 15 patients of whom 10 were female and 5 were male. The predilection of the disease for the female sex is also borne out in the literature. Ages ranged from 2 to 53 years. Most of the patients (12) were less than 30 years old, and the largest single age group was the third decade, in which decade alone were 8 patients. Neither occupation nor social factors played an apparent rôle. Study of the seasonal incidence in our series showed a remarkable restriction of the onset of the disease to the months between late fall and late spring.

**Symptomatology.** In all but 3 of the cases initial symptoms were preceded by an acute infectious disease, the nature of which in each case is indicated in Table 1. Predominance of infections of the respiratory tract (influenza, tonsillitis, scarlet fever) is conspicuous. The interval between invasion by the antecedent disease and the first appearance of edema varied from a few days to 6 weeks. During this period of "incubation" or latency 2 patients complained of general weakness and malaise, and 2 others experienced mild articular pains. In most of the cases, however, the interval was essentially asymptomatic, the patient having been regarded as normally convalescent or entirely recovered from the recent infection when the cutaneous signs characteristic of scleredema presented themselves. So far as could be determined, the onset of scleredema was at no time accompanied by fever.

Swelling started on the necks (often initially regarded as "stiff neck") of 12 patients, on the faces of 2, and over the abdomen of 1. Usually, the involvement spread rapidly to occupy extensive portions of the body, in 6 cases becoming generalized. In the other cases the disease was confined to the upper portions of the body, extending down to the abdomen or buttocks and including, in 2 instances, the thighs. Even in cases of generalized distribution, the lower extremities were often involved but slightly. Edema conspicuously spared the feet in every case, and the hands in every case save 1. As a rule the evolution was rapid, requiring less than 1 week or 2 for completion, but in 2 cases the edema spread more slowly, over a period of 2 to 3 months. When the patients were seen at the clinic, the disease in all cases had already attained its definitive extent.

The affected skin subjectively was described as stiff or rigid and restraining. Movements of affected parts were thereby materially restricted. Pain was notably absent, and in only 2 instances were paresthesias experienced. The degree of stiffness and edema was observed by 2 patients to fluctuate from day to day, and in 1 instance the patient noticed exaggerated tightness during the week preceding the menses. Occasionally, a patient reported dyspnea on exertion, caused by constriction about the neck or thorax, and in a few instances symptoms of slight dysphagia or hoarseness were present.

One patient experienced weakness and tenderness of the muscula-

ture of the extremities and shoulder girdle. Although biopsy was not performed, it was considered likely that muscular involvement by the disease had supervened.

The appearance of the skin was sometimes deceptive, in that few abnormalities were visible on casual inspection. The surface usually revealed no sheen or prominence of follicles. The minute markings were generally preserved, except in a few cases which displayed a smooth, glossy, pseudo-atrophic appearance. The color was at times pale, although the pallor was not striking, and the glazed ivory or alabaster hue of scleroderma was entirely lacking. One patient exhibited diffuse light brownish discoloration over the affected portions, and another presented discrete plaques of hyperpigmentation over the extremities. In most cases the face appeared somewhat puffy, and the deeper folds were diminished or obliterated, bestowing a "masked" appearance on the patient. The eyelids were usually not swollen. In 2 cases the tongue was involved, with consequent restriction of movement.

On palpation, an unanticipated degree of change was usually elicited. The skin provided a sensation of thickness, of deep, resistant, lardaceous or brawny induration, and it could not be picked up in large folds or moved freely over subjacent tissues (Figs. 1 and 2). Instead, it appeared usually to be fused with or bound inflexibly to the subcutis, as if it were either congealed or in a state which has been appropriately compared to the state produced by homogeneous infiltration of the deeper layers with paraffin.<sup>16</sup> No pitting resulted from firm pressure. The borders of involvement were not distinct; merging took place gradually with the normal skin.

Two patients had mild cyanosis of the otherwise unaffected fingers and toes, and they complained of numbness and tingling in the distal parts of the extremities. Another patient showed cyanosis of the fingers only. Although these phenomena might reflect a vasomotor abnormality, the possibility was considered also of superficial venous engorgement induced by the constricting, proximally situated infiltrate. Increased sweating of hands and feet was complained of by these 2 patients, and 1 additional patient exhibited generalized excessive sweating.

The duration of the disease in the case of patients we have been able to follow ranged between 3 months and 3 years. So far as could be ascertained, involution was complete wherever "cleared" or "healed" is indicated in Table 1. Recurrences after healing are not, however, uncommon. Two of our patients furnished such a history, the interval between attacks lasting 2 years in 1 instance, and 20 years in the other.

Laboratory data yielded little of diagnostic significance in our material. Morphologic and chemical constituents of the blood showed no important anomalies. Determinations of the basal

metabolic rate were normal in the 7 instances in which they were performed. The patient suspected of having muscular infiltration by scleredema excreted increased quantities (up to 400 mg.) of creatine as demonstrated by 24-hour specimens of urine.

TABLE 1.—SCLEREDEMA ADULTORUM: SUMMARY OF 15 CASES.

Case.	Age, sex.	Antecedent disease.	"Incubation" interval.	Site of onset.	Development and duration.	Miscellaneous.
1	27 F	Spontaneous abortion	5 weeks	Neck	Spread over chest and arms; nearly clear in 8 mos; slight stiffness of neck remaining	Later pregnancy did not impede involution.
2	37 F	"Rheumatism"	...	Neck	Spread to face, upper trunk and arms; greatly improved in 2 mos.	Recurrence 20 yrs. later, lasted 1 yr.
3	18 M	Influenza, mastoiditis (right)	6 weeks	Right cheek	Generalized in 10 days; healed in 9 mos.	
4	25 M	Influenza, arthritis left knee	1 month	Neck	Extended over head, trunk and upper extremities in 5 days; cleared in 6 mos.	Biopsy.
5	53 F	Infected thyroidectomy incision	6 weeks	Neck, in zone of infection	Generalized; extremities mildly involved. Improved rapidly first 4 mos.; healed within 2 yrs.	Hyperpigmentation. Biopsy.
6	2 M	Scarlet fever, otitis media, mastoiditis	5 weeks	Head, neck, tongue	Rapidly generalized; marked improvement first month; cleared in 8 mos.	
7	39 M	Influenza	2 weeks	Abdomen	Slowly spread to neck, face, tongue, arms, trunk and thighs; healed in 3 mos.	Slight dysphagia and hoarseness. Pigmented plaques over extremities.
8	6 F	None?	...	Neck	Rapidly generalized; recovered in 1 yr.	Biopsy.
9	20 F	None	...	Neck, elbows	Slowly generalized; cleared in 3 yrs.	Slight dyspnea and hoarseness. Cyanosis, hyperhidrosis and numbness, hands and feet. Biopsy; recurred 1 yr. later; rapid involution.
10	25 F	Tonsillitis, cervical lymphadenitis	1 month	Neck	Spread to face, trunk, upper extremities and thighs. Moderately improved 1 yr. later	Numbness, cyanosis, hyperhidrosis, hands and feet. Biopsy.
11	6 M	Measles	2 weeks	Face	Slowly generalized. Healed in 3 mos.	
12	20 F	None	...	Neck	Spread to face, upper extremities and chest in several days	Fingers cyanotic.
13	27 F	Influenza	1 month	Neck	Extended slowly over shoulders and chest. Healed in 8 mos.	
14	26 F	Tonsillitis, otitis media	2 weeks	Neck, cheeks	Spread to face, trunk, upper extremities (including hands). Stationary after 4 mos. Improved in 7 mos.	Pregnant (7 mos.) at onset; increased stiffness postpartum. Slight dysphagia; hyperhidrosis.
15	29 F	Scarlet fever	1 month	Neck	Spread to face, scalp, trunk and arms. No improvement after 2½ yrs.	Muscular tenderness and weakness, dyspnea, creatinuria.

**Pathologic Considerations.** Specimens of skin were excised for microscopic examination from 5 patients. Study of the sections

prepared by routine histologic methods revealed few striking abnormalities. The epidermal outline exhibited the usual undulatory pattern, indicative of the delicate wrinkling which usually persists over the cutaneous surface. The epidermis itself presented no significant changes aside from hyperkeratosis and follicular plugging in several sections. In the cutis the chief findings were disclosed in the middle and deep portions, where the collagen bundles were somewhat swollen here and there, often staining homogeneously and separated by clear spaces (Fig. 3). Alterations in connective tissue were not, however, especially outstanding; 2 specimens, indeed, showed no deviation from the normal. In only 1 instance was the pars papillaris moderately homogenized. A distinct perivascular infiltrate occurred at times, the cells consisting mostly of lymphocytes and fibroblasts. In 1 case mild swelling was observed in a few of the vascular walls, and in another a number of vessels occupying the lower cutis and subcutis were dilated. There was no morphologic disturbance of the lymphatic vessels. Cutaneous appendages appeared also to be intact, although in one section hair follicles and sebaceous glands were atrophic. The elastic tissue in general revealed no peculiarities; nor were changes demonstrable in the cutaneous nerves or in the subcutaneous fatty tissue. Biopsies of muscular tissue, obtained from 2 patients, showed a normal structure.

Freund,<sup>6</sup> in 1930, was able by special fixation and staining to demonstrate in the interstitial edematous spaces a net of metachromatic "mucin-like" substance which he believed was, like mucin, a glycoprotein. In our formalin and alcohol-fixed tissue, this metachromatic tinctorial reaction could not be produced. The substance contributing to the edema is not in a fluid state, because incision of the skin does not cause its exudation.

**Differential Diagnosis.** The most important single problem of diagnosis is encountered in early diffuse scleroderma. In the literature scleroderma and scleredema have been repeatedly confused, as the paper by Touraine and his associates testifies with abundant documentation. In the primary, edematous stage of diffuse scleroderma, differentiation from scleredema may at first be difficult or impossible,<sup>12</sup> for the skin at such a stage exhibits a firm swelling similar to that caused by scleredema, and which also may follow in the wake of a previous infection. Nor may the histopathologic changes of scleroderma be sufficiently distinctive at this time to be of aid.

Prodromal articular and vasomotor symptoms often usher in diffuse scleroderma.<sup>13</sup> Earliest signs consist in gradual diminution of the normal folds, waxy or glossy sheen of the skin, and a loss of facial expression; sclerodactylia, also, may appear shortly. The color assumes an ivory tint. Induration, however, does not spare the superficial portion of the skin, as it usually does in scleredema.

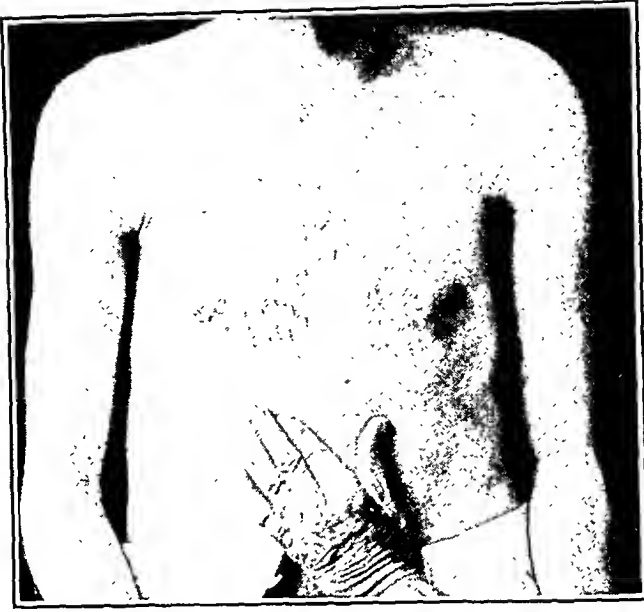


FIG. 1.—(Case 4.) Scleredema adultorum of 5 weeks' duration, showing increased consistency of the skin which resists manipulation.



FIG. 2.—(Case 9.) Scleredema adultorum which had been present for 8 months. The superficial wrinkling produced by attempts to pick up the skin indicates the characteristic deep induration of this disease.





FIG. 3.—Skin from abdomen of a patient (Case 9), showing perivascular infiltrate in the upper cutis, homogenization of collagen, and edematous spaces between collagen bundles (hematoxylin and eosin.  $\times 60$ ).

Later, the characteristic picture of hidebinding and atrophy is seen, with rigid, shrunken, mask-like facies, limitation in movements of the mouth and tongue, wasting of subcutaneous tissue and muscles, restricted mobility of joints, and bronzing of the skin. This relentless, progressive, atrophic development does not occur in scleredema. The essential histopathologic changes consist of vascular thickening with obstruction of the lumens, perivascular cellular infiltration, and hypertrophy and sclerotic homogenization of collagen.

Dermatomyositis<sup>14</sup> early in its course likewise may at times imitate scleredema closely. One of us (O'Leary<sup>12</sup>) has called attention to this possibility on several occasions. The fact that the pathologic process in scleredema sometimes invades the musculature can render its resemblance to dermatomyositis all the stronger. Indeed, it may be necessary in certain cases to reserve judgment until the course of the disease has been observed over a reasonable length of time, because even biopsy may give indefinite results. Dermatomyositis may be heralded by muscular (weakness, tenderness, and pain), cutaneous (edema, eruption), or vasomotor (acrocyanosis or Raynaud-like) signs. The vulnerability of the muscles of the shoulder and pelvic girdle, the arms and thighs, and the neck is outstanding, and atrophy almost always develops in the affected groups. Implication of the vital striated musculature of the pharynx, larynx, thorax, and diaphragm constitutes the most serious complications of dermatomyositis. Cutaneous manifestations include edema, which may simulate closely that of scleredema, erythema, diffuse or patchy hyperpigmentation, sclerodermic thickening, lupus erythematosus-like efflorescence and poikiloderma atrophicans vasculare. Fever may be an accompaniment of dermatomyositis, although if it is present, it is usually of moderate grade. As noted before, fever is absent in the evolution of scleredema. Dermatomyositis follows a progressive course, often without remissions, to a certain stage, after which, if the patient survives, activity may cease. The disease terminates fatally in approximately one-half the cases. Recovery, when it occurs, is usually partial or is marked by residua such as muscular atrophy and incapacity as well as cutaneous sclerosis, pigmentation, and calcification.

It is doubtful if other conditions which may superficially resemble scleredema need be confused if concomitant features are properly appraised. Such diseases, listed here mostly for academic purposes, include myxedema, lymphedema, angioneurotic edema, hereditary trophedema, cardiorenal edemas, and elephantiasis. Sclerema neonatorum and edema neonatorum<sup>3a,8</sup> are rare, usually fatal diseases of newborn infants characterized by abnormalities in the subcutaneous tissues, and are accompanied by serious constitutional symptoms. Fox<sup>5</sup> has clearly differentiated these diseases from the benign, self-limited subcutaneous fat necrosis of newborn or young infants.

**Treatment.** Although claims for any recommended therapeutic regimen may rightfully be challenged in the light of the self-limited character of scleredema, we concur in the belief that the cutaneous picture can be influenced favorably by certain agents. We shall mention briefly our experience in the management of this series of cases. Since there is no interference, as a rule, with general health, restrictions need not be imposed upon the patient's activity. If feasible, foci of infection should be eradicated. It is our opinion that in 3 instances the disease was materially ameliorated by the removal of septic teeth or tonsils (this experience would suggest that sulphanilamide might possibly be deserving of trial). Thyroid was administered to several patients in an attempt to hasten involution by accelerating the peripheral circulation, but without impressive response. Our most valuable results were obtained, we believe, with induced fever, either alone or in combination with physiotherapeutic procedures. Fever was induced by means of typhoid vaccine injected intravenously and repeated at intervals for as long as visible improvement was forthcoming. Hyperthermia sessions were employed in 2 instances. Softening and increased pliability of the skin of several patients could be demonstrated shortly after one or a few febrile bouts. Radiant heat, ultraviolet irradiation and judicious massage are effective auxiliary measures.

**Comment.** Precedence of scleredema by some acute infection is a nearly constant feature of the disease. Among such infections influenza, tonsillitis, measles, scarlet fever, mumps, otitis, erysipelas, and impetigo have been recorded. Then ensues a short interval lasting usually 2 or 3 weeks, during which the patient as a rule is free of symptoms, although vague aches and pains are sometimes experienced. Early in scleredema there may be an associated erythematous eruption, but this is exceptional and was not noted by any of our patients. In the majority of cases, the first abnormality which ushers in the disease is the peculiar deep edema and stiffness in the posterior or lateral cervical region. This change extends upward to include the adjacent skin of the neck, face and scalp, and downward over the shoulders, arms, trunk and, in fewer cases, the lower extremities. Nearly always the hands and feet remain unaffected. The tongue may be included in the involvement, as may also the general skeletal musculature.<sup>2</sup> Progression of the disease is usually complete in 2 or 3 weeks, although it sometimes requires a longer interval, and the condition, once established, remains stationary for a variable time, generally a period of several months, before involution begins. Depending on the extent of involvement, the patient may experience limitation of movement of the extremities, slight respiratory embarrassment, immobility of facial expression, dysphagia and general weakness. The duration of the disease is inconstant; some cases have been reported in which the disease cleared within a few days; other instances of the disease

have persisted for many years. Atrophy does not result. Touraine, Golé and Soulignac were convinced that cutaneous infiltration sometimes persists almost indefinitely in circumscribed portions, and that therefore the idea that complete clearing is a criterion for cure of scleredema is fallacious. Recurrences following recovery, as well as residua in the form of indurated cutaneous regions, are probably not uncommon.

The nature of the process is still a mystery. Buschke considered the possibility that diffuse disease of the lymphatic vessels might be a factor in the pathogenesis of scleredema. Touraine and his associates also supported the theory of direct, although attenuated, infection. They contended that cutaneous infiltration commences in the zone of primary infection, and since this zone is generally pharyngeal, the first appearance occurs in the region of the lymphatic drainage in the neck. The involvement, according to them, progresses in a manner analogous to that of erysipelas. Some substantiation for this theory may possibly be interpreted from our Cases 3 and 5.

Touraine and his associates have proposed to catalog scleredema, scleroderma and dermatomyositis under the inclusive title of "extensive benign sclerodermiform cellulitis." This term would signify a special type of inflammation of the cellular tissues of the cutis and subcutis with occasional deeper extension to the fasciæ and muscles. The aforementioned authors placed great emphasis on certain superficial attributes which the three diseases share in common. But to us there is an inadequate factual foundation for the thesis of these investigators, which seems to be largely supported by anomalous, presumptively "transitional" forms, unifying this group of so-called dermatoscleroses. Gottron<sup>7</sup> and Grzybowski<sup>9</sup> also have discussed certain clinical and histologic relationships of dermatomyositis to scleredema.

Disease of the cutaneous nerves has been suggested as an etiologic possibility,<sup>11</sup> and the alleged relationship of scleredema to trophedema has been discussed recently by Helfand.<sup>10</sup> The existence of a diffusible toxin which acted on the collagen was postulated by Sellei.<sup>17</sup> Endocrine disease has been incriminated as a possible factor in scleredema,<sup>3b</sup> as it has, with as little justification, in numerous other dermatoses. A vague similarity of scleredema to myxedema might be conjectured on pathologic grounds,<sup>15</sup> and an analogy to the somewhat limited distribution of scleredema may doubtfully exist in localized myxedema. The relationship of the infiltrating material in scleredema to the mucin it appears to resemble must await further elucidation. Until more is known of the histochemical nature of the cutaneous alterations occurring in scleredema, speculation in regard to pathogenesis is fruitless.

**Summary.** An analysis is presented of the clinical and pathologic features of 15 cases of scleredema adultorum in which the patients

were observed at The Mayo Clinic. The distinctive involvement of tissue and benign course are described, and other qualities are surveyed which distinguish the disease from diffuse scleroderma and dermatomyositis. Our experience with various agents of treatment is summarized. Probably the involution of scleredema may be accelerated by certain therapeutic procedures, even though the exact nature of the morbid process is for the present unknown. Theories of pathogenesis are reviewed.

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## THE LYSOLECITHIN FRAGILITY TEST.

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THE commonest test for the fragility of the red blood cells is based on the use of various concentrations of hypotonic salt solution. That the same red blood cells may behave differently towards different lysins is not generally appreciated. Thus according to Ponder,<sup>25</sup> who stresses the so-called Rywoseh series, the red cells of different species behave in diametrically opposite ways to solutions of saponin and to hypotonic solutions of sodium chloride. The reaction of abnormal red cells to different lysins has been but little studied. In the course of previous work with the presence of lysolecithin in the blood of various normal and abnormal conditions, the reaction of the abnormal red blood cells of congenital hemolytic jaundice was studied. It was soon recognized that the spherocytes of this disease were unusually fragile to this lysin and that this reaction might be of some importance in diagnosis.

Congenital hemolytic (spherocytic) jaundice is characterized clinically by anemia, increase in reticulocytes, enlarged spleen and the signs of increased blood destruction (icterus, increased bilirubinemia, increased excretion of pigment in the urine and feces). Three further symptoms call for particular attention, namely: 1, the spherocytosis of the erythrocytes; 2, the decreased resistance of the red cells to hypotonic solutions of sodium chloride; and 3, the evidence of inheritance.

Spherocytosis is due to a decrease of the mean cell diameter with simultaneous increase of the mean thickness diameter. This change of form is considered by most authors (Naegeli,<sup>23</sup> Gänsslen,<sup>12</sup> Haden<sup>13</sup>) as pathognomonic of congenital hemolytic jaundice. Thus Thompson<sup>27</sup> (1936) says: "The spherical microcytes . . . are as pathognomonic of this disease as are the sickle cells in sickle-cell anemia." Naegeli terms the disease "globe-cell anemia"; Krumbhaar<sup>17</sup> calls it "spherocytic jaundice." On the other hand, von Boros,<sup>3</sup> Heilmeyer<sup>15</sup> and Dameshek and Schwartz<sup>7</sup> describe the presence of spherocytes in various conditions. The latter authors found that spherocytosis was common to various hemolytic syndromes and on the basis of clinical and experimental observations concluded that this abnormality of the red cells was due to the action of various hemolytic agents upon the erythrocytes.

Increased fragility of the erythrocytes to solutions of hypotonic saline has also been regarded since the time of Chauffard<sup>5</sup> (1907) as pathognomonic of this disease. Haden<sup>13</sup> pointed out the direct correlation between spherocytosis and decreased NaCl resistance. However, Gänsslen,<sup>12</sup> who studied more than 100 cases, stated that in more than 10% of the cases the hypotonic salt resistance was normal. Furthermore, hemolytic anemia of other types, completely distinct from congenital hemolytic jaundice, also showed increased saline fragility.

The evidence of inheritance is of importance in diagnosis. The disease frequently remains quite latent, however, and only with the most careful hematologic methods can deviations from the normal be ascertained (Paschkis,<sup>24</sup> Gänsslen<sup>12</sup>). Hemolytic anemia may occur in the course of other diseases as so-called symptomatic forms. These cases have been observed in association with various exogenous and endogenous toxic influences. In this group belong the cases of sepsis from gas bacilli and streptococci (Widal<sup>27</sup> and his school), Hodgkin's disease of the spleen (Holler,<sup>16</sup> Davidson,<sup>8</sup> Singer<sup>26</sup> *et al.*), lymphatic leukemia (Paschkis,<sup>24</sup> Klima<sup>17</sup>) and of lead poisoning (Davidson,<sup>8</sup> etc.).

In addition to these symptomatic cases, is the group of cases of acute hemolytic anemia without congenital or familial background, and without obvious cause. Widal, Abrami and Brulé<sup>28</sup> described these cases as acquired hemolytic icterus; Chauffard<sup>5</sup> and his co-workers demonstrated the presence of serum hemolysins in certain

of them; Lederer<sup>10</sup> described them as a "new" disease; and more recently Dameshek and Schwartz<sup>7</sup> noted the presence of isohemolysins and the dramatic effect of splenectomy. In all of these cases of non-congenital, acquired hemolytic icterus, spherocytosis and increased saline fragility may be prominent features.

The establishment of spherocytosis in a case of hemolytic anemia is of essential importance. This is done by direct examination of the stained smear, and, as Dameshek<sup>6</sup> has recently shown, by studies of rouleaux formation and of "cupping" and so on in fresh preparations. Calculation of the mean cell diameter, the mean cell volume and the mean thickness diameter of the erythrocytes, although valuable, is laborious. In view of the recent investigations of Dameshek and Schwartz,<sup>7</sup> which demonstrate conclusively that spherocytosis cannot be considered as pathognomonic of the *congenital* hemolytic type, a test which discriminates between the spherocytes of the congenital and of the other types would be of some value. This paper deals with such a test, which is based upon the reaction of the red cells to a substance called "lysolecithin" derived from blood serum. Elaboration of the method was stimulated by the studies of Bergenhelm and Fåhræus.<sup>2</sup>

The Researches of Bergenhelm and Fåhræus. Three years ago these Swedish investigators reported the discovery of a new hemolysin in normal blood. They found that if defibrinated or citrated blood was allowed to stand quietly for several hours at body temperature, characteristic changes were produced: 1, considerable retardation of the sedimentation rate of the erythrocytes; 2, a change from the biconcave to the *spherical* form; 3, a noticeable reduction of aggregation (rouleaux formation). These changes, they concluded, were due to a modification of the serum. They found that serum contained a lecithinase, which was capable of splitting a substance from the serum lipoids; adsorption of this latter substance by the red blood cells resulted in the above changes. This enzymatic process reached its maximum at a temperature of 42° C. and a pH of 7.2 and was inactivated at 56° C. The substance, formed in undisturbed blood at a temperature of 37° C., was found to be identical with the so-called lysolecithin. Lysolecithin is a definite chemical substance, which has received prominence in the study of the biologic effects of snake venom. Flexner and Noguchi<sup>11</sup> were the first to show that blood serum was necessary in the hemolysis of red blood corpuscles by cobra toxin; red cells washed free of serum were incapable of lysis. Kyes and Sachs<sup>10</sup> found that the hemolytic effect of cobra toxin was activated by the presence of lecithin without serum being present. Further experiments (Lüdecke,<sup>21</sup> Manwaring,<sup>22</sup> Delezenne and Ledebt<sup>9</sup>) elucidated the mechanism of the action of this toxin. In the venoms of the cobra, scorpions, and of bees a lecithinase is present which splits from the lecithin molecule the unsaturated fatty acid group. The resulting residue is the hemolyzing lysolecithin. Chemically,

this substance is characterized by insolubility in ether and by ready solubility in water or alcohol.

The globular or spherocytic form of the erythrocytes produced by the adsorption of serum lysolecithin is in all probability the forerunner of hemolysis. At a stronger concentration of lysolecithin, complete hemolysis of the erythrocytes occurs. The amount of lysolecithin in freshly prepared normal serum is fairly low, amounting on the average to about one-fourth of the concentration which results when the undisturbed serum is kept at 37° C. for 24 hours.

In congenital hemolytic jaundice the circulating erythrocytes are either partly or wholly spherocytic. Since a dilute solution of lysolecithin renders the normal disk-shaped erythrocytes spherocytic, but a more concentrated solution leads to hemolysis, the question arises whether in hemolytic jaundice, the spherocytic cells are not more readily hemolyzed by lysolecithin than are normal erythrocytes. In order to decide this question, it was necessary first of all to possess an exact process for the extraction of serum lysolecithin, as well as an accurate method for determining its quantity.

**Methods.** Lysolecithin is prepared as follows: *At least 20 cc. of animal (horse or dog) or human serum are warmed at rest for 24 hours (incubator) at 37° C. in order to obtain a maximal quantity of lysolecithin. The serum is then precipitated with 10 times its quantity of 95% alcohol, filtered and the filtrate evaporated in a vacuum apparatus at room temperature to complete dryness. The residue is again dissolved in a little alcohol, mixed with 6 times its quantity of ether and placed in the refrigerator overnight. The precipitate contains the lysolecithin. After removing the ether and drying the precipitate the content of lysolecithin is determined.*

For this determination its hemolytic power is used. The quantity that is to be ascertained is dissolved in 0.8 cc. of physiologic salt solution. From this basic solution a geometric series of dilutions is prepared in the usual manner by further dilution with physiologic solution of NaCl. An approximate 2% saline suspension of washed erythrocytes containing about 100,000 cells per c.mm. is taken up in leukocyte pipettes to the 1 mark and diluted with the various single dilutions of lysolecithin to the 11 mark. While hemolysis is taking place, the pipettes are set aside for 1 hour. With extremely weak concentrations of the lysis, the reaction may be facilitated by placing the pipettes in the incubator for the same period. The solutions are then examined in a hematocytometer. By determining the number of undissolved erythrocytes an exact measure of the degree of hemolysis is obtained. Hemolysis above 90% is regarded as complete. The evaluation of exactly equal quantities of lysolecithin with the same amount of normal human erythrocytes always gives similar results, as has been proved by numerous experiments. If heterogenous erythrocytes are used the results may be entirely different. This is best shown in Table 1, in which the hemolytic power of 2 equally large quantities of lysolecithin has been measured both with human and dog erythrocytes.

TABLE 1.—COMPARATIVE HEMOLYTIC EFFECT ON HUMAN AND DOG ERYTHROCYTES.

Amount of hemolysis in %.	Lysolecithin dilution.							
	1:2.	1:4.	1:8.	1:16.	1:32.	1:64.	1:128.	1:256.
Human erythrocytes	+	+	+	+	—	—	—	—
	100	100	100	98	42	0	—	—
Dog erythrocytes	+	+	+	+	+	+	+	—
	100	100	100	100	100	100	100	58
								0



The table shows that dog erythrocytes are much less (8 times less) resistant to lysolecithin than human ones. The test may likewise be used in the differential diagnosis of various hematologic cases, particularly when there is a question of congenital hemolytic jaundice. Equal quantities of lysolecithin are tested against the same amount of both normal and questionably abnormal erythrocytes. The dried lysolecithin (ether residue) from at least 20 cc. of unmoved incubated serum is dissolved in 1.6 cc. of normal saline. The solution is divided in equal parts and from these initial solutions the geometric series of dilutions is prepared.

For smaller quantities of lysolecithin, the method may be modified still further. For this purpose the test is made in special pipettes that take just one-half the contents of the normal leukocyte pipettes. The amount of serum used for the lysolecithin extraction can thus be reduced to 10 cc. The dried lysolecithin for each test is dissolved in 0.4 cc. of normal salt solution.

**Results. A. Normal Cases.** As numerous tests (30 cases) have proved that normal human erythrocytes always show the same resistance towards lysolecithin, the resistance of the spherocytes of congenital hemolytic jaundice has been determined in comparison with the normal. In order to give clear expression to the results, the tests have always been made with a concentration of lysolecithin that gives complete hemolysis up to the dilution 1 to 8. Of the normal cases, all of which showed the same results, 6 cases are included in Table 2.

**B. Congenital Hemolytic Jaundice.** As Table 2 shows, the resistance of the red cells of congenital hemolytic jaundice to lysolecithin is definitely less than that of the normal ones: whereas the normal cases show at most incomplete hemolysis at a lysolecithin dilution of 1 to 16, the cells of congenital hemolytic jaundice showed complete hemolysis at this dilution and in some cases there was more or less incomplete hemolysis at a dilution of 1 to 32. One case (No. 9) showed complete hemolysis at 1 to 32 and a high degree of incomplete hemolysis at 1 to 64. These values are the more remarkable when it is considered that the lysolecithin fragility test is made with a *geometric* progression of dilutions rather than with an arithmetic one, as in the fragility test with hypotonic solutions of sodium chloride.

To characterize the cases the following may be added. Cases 1 to 3 all came from one family and showed the typical symptoms of congenital hemolytic jaundice. The same applies to Case 4, who was aware of the character of his illness and of its familial character. In Case 5 the hereditary features were poorly defined. The father of the patient had died of pneumonia at an early age and the mother could not remember any symptoms characteristic for hemolytic jaundice in her husband. The examination of the mother showed completely normal hematologic conditions. The patient (an only

TABLE 2.—LYSOLECITHIN RESISTANCE OF NORMAL AND SPHEROCYTIC ERYTHROCYTES OF CONGENITAL HEMOLYTIC JAUNDICE.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.						Result.
				1:2.	1:4.	1:8.	1:16.	1:32.	1:64.	
	Hypertension	Normal	0.45-0.30	+ 100	+ 100	+ 92	- 26	- 0	-	Normal
	Normal case	Normal	0.45-0.30	+ 100	+ 100	+ 92	- 22	- 0	-	Normal
	Diabetes	Normal	0.45-0.32	+ 100	+ 100	+ 97	- 34	- 0	-	Normal
	Normal case	Normal	0.45-0.28	+ 100	+ 100	+ 92	- 19	- 0	-	Normal
	Hypertension	Normal	0.45-0.30	+ 100	+ 100	+ 97	- 38	- 0	-	Normal
	Normal case	Normal	0.45-0.30	+ 100	+ 100	+ 95	- 23	- 0	-	Normal
1	Hemol. jaund., man aged 49 yrs.	Hb. 50 E. 2.9 Retic. 9.0%	0.60-0.30	+ 100	+ 100	+ 100	+ 91	- 28	- 0	De- creased
2	Hemol. jaund., daughter of Case 1, aged 20 yrs.	Hb. 60 E. 3.3 Retic. 11%	0.55-0.30	+ 100	+ 100	+ 100	+ 93	- 20	- 0	De- creased
3	Hemol. jaund., son of Case 1, aged 14 yrs.	Hb. 54 E. 3.0 Retic. 7.8%	0.55-0.30	+ 100	+ 100	+ 100	+ 98	- 56	- 0	De- creased
4	Hemol. jaund., man aged 42 yrs.	Hb. 90 E. 4.2 Retic. 8.4%	0.64-0.56	+ 100	+ 100	+ 100	+ 93	- 49	- 0	De- creased
5	Hemol. jaund., boy aged 17 yrs.	Hb. 64 E. 3.6 Retic. 8.2%	Normal 0.45-0.30	+ 100	+ 100	+ 100	+ 92	- 60	- 0	De- creased
6	Hemol. jaund., girl aged 12 yrs.	Hb. 70 E. 3.6 Retic. 18%	0.80-0.30	+ 100	+ 100	+ 100	+ 100	- 38	- 0	De- creased
7	Hemol. jaund., mother of Case 6	Hb. 82 E. 4.4 Retic. 2.6%	Normal 0.45-0.30	+ 100	+ 100	+ 100	+ 96	- 51	- 0	De- creased
8	Hemol. jaund., man aged 50 yrs.	Hb. 106 E. 4.9 Retic. 7%	0.76-0.04	+ 100	+ 100	+ 100	+ 92	- 75	- 35	De- creased
9	Hemol. jaund., son of Case 8, aged 14 yrs., splenect.	Hb. 95 E. 4.8 Retic. 0.2%	0.60-0.04	+ 100	+ 100	+ 100	+ 98	+ 90	- 55	De- creased
10	Hemol. jaund., dghtr. of Case 8, aged 6 yrs., splenect.	Hb. 90 E. 4.4 Retic. 0.4%	0.68-0.16	+ 100	+ 100	+ 100	+ 94	- 79	- 36	De- creased

child) presented the signs of hemolytic anemia and had a large spleen. The mean diameter of the erythrocytes was  $6.9\mu$ . The resistance of the red cells against hypotonic salt solution, determined several times, was normal. Despite this, the lysolecithin fragility was a pathologic one. Case 6 is a girl of 12, who since  $1\frac{1}{2}$  years has had a large spleen, moderate enlargement of the liver, slight icterus and symptoms of hemolytic anemia. The greatly increased fragility of her erythrocytes towards hypotonic salt solution, the marked reticulocytosis as well as the high degree of urobilinogenuria indicated a hemolytic jaundice. The lysolecithin reaction confirmed the diagnosis. The anamnesis concerning the hereditary conditions, however, proved quite negative. The history, clinical and hematologic examination of the parents and of 2 brothers and sisters showed totally normal conditions, except that the number of reticulocytes was slightly increased in the mother. In spite of *normal* saline fragility of the erythrocytes the mother showed a high pathologic lysolecithin reaction. Thus the hereditary connections were also established in this case. The last 3 cases are all members of one family. The 2 children were splenectomized 2 years previously, as an emergency measure for severe hemolytic crises. As the splenectomized cases also showed a pathologic lysolecithin reaction, 1 case giving the most pronounced reaction of these series, it must be assumed that the abnormal fragility of the erythrocytes towards the serum lysin remains unchanged after splenectomy, although the fragility to hypotonic solutions of sodium chloride is sometimes considerably altered.

*C. Acquired Hemolytic Anemia.* The results of the lysolecithin fragility test in the non-congenital types of hemolytic anemia are seen in Table 3.

CASE 1 should be discussed in detail. This patient, aged 45, 18 years previously had cervical adenitis, which a biopsy proved to be tuberculous. Six years prior to her present illness a mediastinal tumor was discovered and treated with Roentgen rays. Three months before entering the hospital, she became very anemic (Table 3), and numerous spherocytes were present. There was slight jaundice and a firm spleen was readily palpable 2 fingers below the costal margin. The liver was not enlarged. A large mediastinal tumor was again demonstrated. There was no other lymphadenopathy. From the hematologic standpoint the diagnosis was thus hemolytic jaundice. Hemolysis of the red cells to hypotonic saline began at 0.6% NaCl. Despite this pathologic fragility of the erythrocytes, the lysolecithin fragility was twice completely normal. Because of these data, hemolytic jaundice, associated with Hodgkin's disease of the spleen, was assumed. Splenectomy revealed a typical porphyric spleen. After operation, the anemia at first improved and then changed its character to that of a hypochromic type. There was a slight though definite response to iron, but 5 months later large masses of cervical glands appeared and the patient shortly died.

The occurrence of hemolytic anemia in cases of Hodgkin's disease, although rare, has been described by various authors as I pointed

out in another paper in 1936. Holler and Paschkis<sup>16</sup> (1927) reported a similar case with increased saline fragility and which likewise was submitted to splenectomy because of the diagnosis of congenital hemolytic jaundice. The normal lysolecithin fragility in the case reported above, in association with an abnormal saline fragility, proved valuable in the differentiation of the symptomatic from the constitutional form of hemolytic jaundice.

TABLE 3.—LYSOLECITHIN RESISTANCE IN OTHER HEMOLYTIC ANEMIAS.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.					Result.
				1:2.	1:4.	1:8.	1:16.	1:32.	
	Normal case	Normal	0.45-0.30	+	+	+	-	-	Normal
				100	100	94	44	0	
1	Hemolytic anemia, Hodgkin's disease of the spleen	Hb. 52 E. 1.8 Retic. 12.6%	0.60-0.35	+	+	+	-	-	Normal
				100	100	92	36	0	
2	Hemolytic anemia, lymph. leukemia	Hb. 25 E. 1.1 Retic. 13.8%	0.60-0.28	+	+	+	-	-	Normal
				100	100	98	29	0	
3	Hemolytic anemia, lymph. leukemia	Hb. 34 E. 1.77 Retic. 8.3%	0.72-0.28	+	+	+	-	-	Normal
				100	100	100	55	0	
4	Pernicious anemia	Hb. 50 E. 1.6 Retic. 1%	0.45-0.30	+	+	+	-	-	Normal
				100	100	91	27	0	
5	Pernicious anemia	Hb. 40 E. 1.8 Retic. 0.3%	0.45-0.30	+	+	+	-	-	Normal
				100	100	94	32	0	
6	Pernicious anemia	Hb. 30 E. 0.94 Retic. 0.7%	0.45-0.30	+	+	+	-	-	Normal
				100	100	100	39	0	

CASE 2, a woman, aged 50, showed marked pallor several weeks before admission to the hospital. Examination showed a subicteric patient with a high degree of hemolytic anemia. The spleen was considerably enlarged, but there was no peripheral lymphadenopathy. The white cell count was 11,500 (88% small lymphocytes). The platelets were greatly reduced. Occasional nucleated red cells were seen, together with many small, dense-appearing microcytes (spherocytes). Sternal puncture revealed well-marked lymphoid infiltration of the bone marrow. Fragility of the red cells was increased to 0.6% of hypotonic saline, but the lysolecithin fragility was normal. The diagnosis of subleukemic lymphatic leukemia with symptomatic hemolytic jaundice was made.

CASE 3 showed a similar picture. A man, aged 70, showed a hitherto unrecognized chronic lymphatic leukemia which at the time of hospital admission was associated with acute hemolytic anemia. There was slight icterus, highly positive Van den Bergh reaction in the serum and increased

urobilinogen in the urine. Leukocytes count was: 142,500 of which 92% were mature lymphocytes. Most of the red cells were spherocytes; again the lysolecithin resistance was normal, but the saline fragility was greatly increased.

In 3 cases of pernicious anemia (Cases 4 to 6) with a typical blood picture and excellent response to liver treatment the lysolecithin fragility was normal.

Experiments have thus far indicated that the spherocytes of congenital hemolytic jaundice have a considerably reduced resistance towards lysolecithin, whereas the similarly morphologic spherocytic erythrocytes of other types of hemolytic anemias show a normal reaction to this lysin.

*D. Sicklc-cell Anemia.* In this peculiar congenital condition, which is generally classified as a hemolytic disease, a considerably increased resistance to lysolecithin was observed in 2 of 3 cases. Marked sickling was demonstrable in fresh preparations of the blood of all 3 cases. Hemolysis in hypotonic saline began at a normal level (0.46 to 0.42%) but complete hemolysis was present only at 0.04%, an indication that some of the cells were very resistant to hypotonic salt solution. This fact was recently emphasized by Diggs and Bibb<sup>10</sup> who explain the increased resistance of the cells in sickle-cell anemia by the ability of these erythrocytes to alter their shape without placing their membranes under sufficient tension to cause hemolysis. More recent studies, particularly by Barrett,<sup>1</sup> have demonstrated that the most resistant cells have the general appearance of a target. It is possible, as Barrett points out, that these cells are the direct opposite of the spherocyte in regard particularly to thickness, and therefore most resistant to various lysins.

There is again, however, a lack of complete parallelism between the resistance of cells in sickle-cell anemia towards hypotonic NaCl and lysolecithin. Thus the erythrocytes of Case 3 presented a normal lysolecithin fragility although the presence of saline resistant cells in this case could be demonstrated.

*E. Chronic Non-hemolytic Jaundice.* In 3 of 6 cases of chronic non-hemolytic jaundice an increased resistance to lysolecithin was found. Two of these cases of chronic non-hemolytic jaundice had cirrhosis of the liver with long-standing icterus. The third case had a cancer of the pancreas with obstructive jaundice lasting for 7 weeks. The saline fragility in these cases was normal. In other cases of chronic non-hemolytic icterus both the lysolecithin and the saline fragility tests were normal. In a few cases, the saline fragility was decreased, although the lysolecithin test was normal. That the biochemical structure of the erythrocytes undergoes changes in chronic jaundice (pachydermia of the erythrocytes) has been known for a long time. Since Chanel<sup>4</sup> (1880) and others it has been accepted that the saline fragility of the erythrocytes is not infre-

quently decreased in obstructive jaundice. Barrett<sup>1</sup> has pointed out that "target" cells are seen frequently in the following conditions: sickle-cell anemia, where they have been first described by Haden and Evans,<sup>14</sup> and after splenectomy severe hepatic disease, particularly with obstructive jaundice.

TABLE 4.—LYSOLECITHIN RESISTANCE IN SICKLE-CELL ANEMIA AND IN CHRONIC NON-HEMOLYTIC JAUNDICE.

Case.	Diagnosis.	State of blood.	NaCl resistance.	Lysolecithin resistance, %.					Result.
				1:2.	1:4.	1:8.	1:16.	1:32.	
	Normal case	Normal	0.48-0.30	+ 100	+ 100	+ 100	- 27	- 0	Normal
1	Sickle-cell anemia	Hb. 53 E. 2.7	0.42-0.04	+ 95	- 70	- 20	- 0	-	Highly increased
2	Sickle-cell anemia	Hb. 61 E. 4.9	0.46-0.04	+ 94	- 75	- 40	- 0	-	Highly increased
3	Sickle-cell anemia	Hb. 43 E. 1.9	0.46-0.04	+ 100	+ 100	+ 92	- 48	- 0	Normal
4	Chronic icterus, liver cirrhosis	Hb. 84 E. 4.5	0.44-0.28	+ 100	+ 100	- 65	- 0	-	Increased
5	Chronic icterus, liver cirrhosis	Hb. 92 E. 4.8	0.46-0.34	+ 100	+ 100	- 72	- 20	- 0	Increased
6	Chronic jaundice, Ca. pancreas	Hb. 91 E. 4.4	0.42-0.22	+ 100	+ 94	- 55	- 0	-	Increased

**Discussion.** The results thus far obtained demonstrate conclusively that the mechanism of lysolecithin hemolysis is different from that of NaCl hemolysis. Though the mechanism of NaCl hemolysis is still not entirely clear, we may assume that in consequence of osmotic differences there first occurs swelling and then bursting of the cell. On the basis of measurements of the cell diameter, Haden<sup>13</sup> demonstrated that normal erythrocytes show an increasing tendency to assume a spherical shape when submitted to decreasing concentration of NaCl.

As Berghem and Fåhræus have demonstrated, lysolecithin likewise leads to spherocytosis, but by a different mechanism. The lysin is apparently directly adsorbed by the cell membrane. The normal disk-shaped erythrocytes are first made spherocytic by lysolecithin before hemolysis takes place. They thus require for complete hemolysis a larger quantity of lysolecithin than the already spherocytic cells of the congenital hemolytic jaundice.

This hypothesis does not explain the fact that definite spherocytes

in conditions other than the *congenital* type of hemolytic jaundice behave in a normal manner to lysolecithin. As Dameshek and Schwartz<sup>7</sup> have recently pointed out, spherocytosis is found in various hemolytic conditions, and is by no means pathognomonic of the familial form of hemolytic anemia. These authors produced spherocytosis of various degrees experimentally in guinea pigs by injecting anti-guinea pig hemolytic serum. These spherocytes also showed an increased saline fragility. The conclusion was reached that spherocytosis was due to the activity of hemolysins and not to an abnormal anatomic peculiarity or to a disturbed formation of cells in the bone marrow. Since increased fragility is a function of the increased thickness of the red cells, it is dependent on the same cause. The conclusion was also advanced that the various hemolytic syndromes were all due to hemolysins, possibly of different types and present in different amounts, functioning slowly in some cases and violently in others. They felt that various blood pictures of the hemolytic anemias, *viz.*, anemia, spherocytosis, increased fragility, were in all probability due to the effects of the varying activity of hemolysins.

Spherocytosis may thus be considered as the morphologic expression of a change in the erythrocytic structure due to the action of different kinds of hemolytic agents. It is a forerunner of hemolysis. As the various hemolysins are of quite different nature, one should expect that the resultant physico-chemical alterations in the structure of the cells might differ. The abnormal resistance of the spherocytes to lysolecithin in congenital hemolytic jaundice, as opposed to that in the acquired types, may therefore be explained by varying alterations in the cell structure, caused by chemically different substances. According to this hypothesis spherocytes, although morphologically similar, may be entirely different from the physico-chemical standpoint.

Although the exact mechanism of lysolecithin hemolysis cannot be explained, the practical importance of the use of lysolecithin in the study of erythrocyte fragility need not be influenced by this fact. The examination of the fragility of red blood corpuscles towards both hemolytic agents may be of value in the often difficult diagnosis of hemolytic anemias, as well as for the demonstration of an hereditary tendency. The chief disadvantage in the use of lysolecithin is that it is not readily available. This disadvantage is, however, more than offset by the possibility of a better differentiation of otherwise very similar clinical pictures.

**Summary.** 1. Berghem and Fåhræus demonstrated that normal blood serum contains a hemolytic substance called "lysolecithin." In sufficiently high concentration complete hemolysis of red blood corpuscles occurred, whereas lesser concentrations of lysolecithin resulted in the development of spherocytosis.

2. A method is described for the extraction of lysolecithin from serum and for quantitative measurement of its hemolytic power. Lysolecithin, when extracted from the serum, may be used as a means of testing red cell fragility.

3. The spherocytes of congenital hemolytic jaundice are much less resistant towards this lysis than normal erythrocytes. This decreased resistance of the erythrocytes is occasionally one of the few demonstrable symptoms of latent forms of congenital hemolytic jaundice.

4. In the spherocytosis of various acquired and symptomatic types of hemolytic icterus, the lysolecithin fragility is normal although the saline fragility is definitely altered.

5. Certain cases of sickle-cell anemia and of chronic non-hemolytic jaundice show an increased resistance to lysolecithin.

6. The lack of parallelism in the resistance of various types of erythrocytes to lysolecithin and to hypotonic salt solution indicates that the mechanism of hemolysis by these hemolytic agents is a different one.

7. As Dameshek and Schwartz have pointed out, spherocytosis may be considered as the morphologic expression of an alteration in the structure of erythrocytes due to the action of different types of hemolytic substances. It is a forerunner of hemolysis. Since the spherocytes of congenital hemolytic jaundice and of various acquired types show a different susceptibility towards lysolecithin, the cell structure of these cells must vary. In other words, spherocytes, although morphologically similar, may be quite different physiologically.

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## NEW INDEXES DEMONSTRATING THE DEGREE OF ANISOCYTOSIS IN HUMAN BLOOD.

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THE calculation of the average diameter of red blood cells enters into the routine of hematologic examinations, due to the considerable importance of the size of these cells in the classification of the anemias. For variations in size of the red blood cells in a given case, "anisocytosis" has been the only word used to express this condition. We propose in this paper the use of new hematologic indexes, denoting the quantitative and qualitative value of anisocytosis.

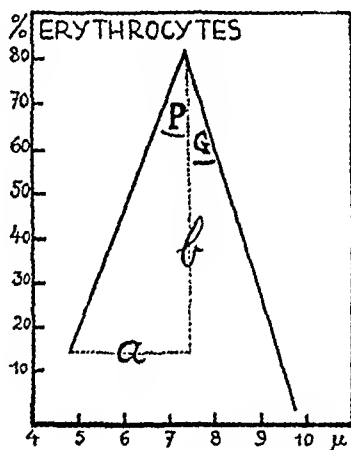


FIG. 1

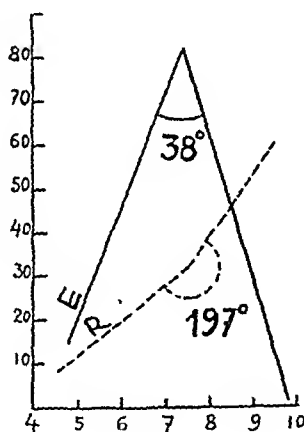


FIG. 2

FIG. 1.—Graphic illustrating method of calculation.

FIG. 2.—Graphic established on the 2d day of observation of a case of pernicious anemia during an anisocytic crisis.

**Technique.** On a glass slide 2 drops of the blood to be examined are mixed with 1 drop of 1% brilliant cresyl blue in Ringer solution. A cover glass with ground polished edges is used in making films of this mixture, which are allowed to dry, and then treated with either Wright's stain or that of the May-Grünwald-Giemsa combination. Thus one obtains preparations showing clearly the contour and normal size of the reticulocytes as well as of the erythrocytes.

**Calculation.** The average diameter of 300 erythrocytes is first established, and the results obtained are placed into three groups. The first, microcytic, comprise the cells of less than 6  $\mu$ . The second here considered as normocytic varies from 6 to 8.3  $\mu$ , whereas the third group, macrocytic, includes the cells larger than 8.3  $\mu$ . The average is thus calculated for each division by the following method. If in the second group the erythrocytes are measured and their diameters found to be 6.3  $\mu$ , 7.2  $\mu$  and 8.2  $\mu$ ,

the number of the erythrocytes of each is multiplied respectively by 6.3, 7.2 and 8.2. The sum of these three multiplications is then divided by the total number of the erythrocytes pertaining to the second group. The result obtained gives the average diameter of the group. From the

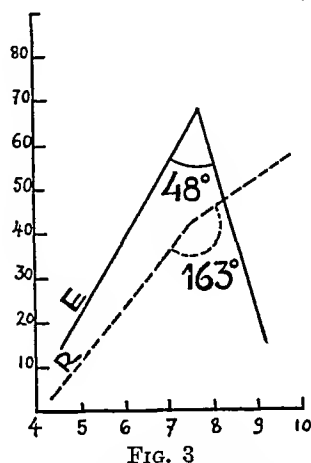


FIG. 3

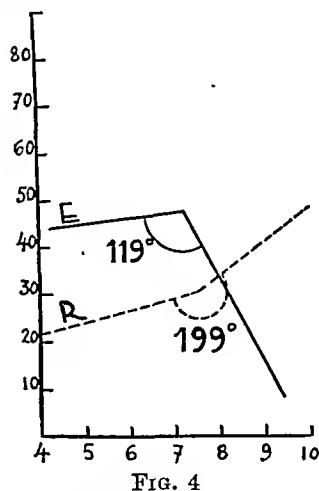


FIG. 4

FIG. 3.—Graphic established on the 5th day of observation of a case of pernicious anemia during an anisocytic crisis.

FIG. 4.—Graphic established on the 12th day of observation of a case of pernicious anemia during a microcytic crisis.

above, it is easy to determine 3 points graphically by inscribing on the abscissa the average diameters of the 3 groups, and on the ordinate, the percentages of the red blood cells. In the example graphically demonstrated, 15% of the cells belonged to the first group with an average diam-

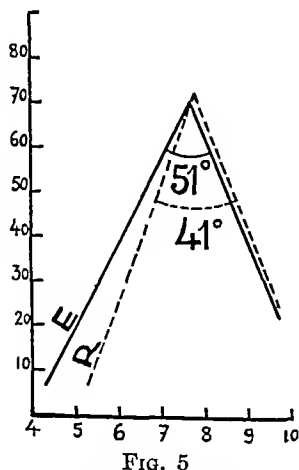


FIG. 5

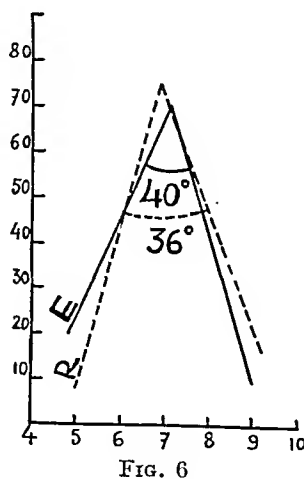


FIG. 6

FIG. 5.—Graphic established on the 16th day of observation of a case of pernicious anemia, *i. e.*, 4 days after the beginning of the treatment.

FIG. 6.—Graphic established on the 21st day of observation of a case of pernicious anemia, *i. e.*, 9 days after the beginning of the treatment.

eter of  $4.8 \mu$ , 82% to the second group with an average diameter of  $7.4 \mu$ , and 3% to the third group with an average diameter of  $9.8 \mu$ . The total angle formed by the two convergent lines represents the quantitative value of anisocytosis. By a vertical line drawn from the summit, this angle is

divided into angle P expressing the microcytic variation; and angle G denoting the macrocytic variation. The partial angles thus represent the qualitative value of anisocytosis. These various angles may be easily represented by their tangents according to the rules of trigonometry.

$$\text{Hence: } \text{Tg. P} = \frac{a}{b} = \frac{\text{difference of the average diameters}}{\text{difference of the percentages}} = \frac{7.4 - 4.8}{8.2 - 1.5} = \frac{2.6}{6.7} = 0.38.$$

By employing trigonometry tables, there is immediately obtained a more concrete value, expressed in degrees, in which the Tg. P. 0.38 corresponds to an angle P of 21 degrees. In the case represented in Figure 1 the Tg. G = 0.30 and the angle G = 17 degrees. Thus the total angle is 38 degrees. Needless to say, the difference between the average diameters of the groups (a) and between the percentages of the blood cells (b) are supplied

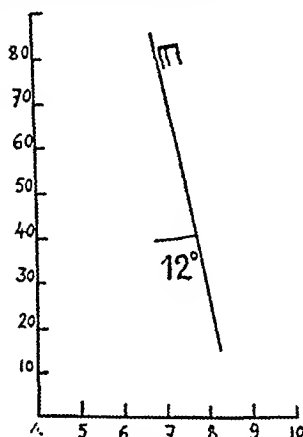


FIG. 7.—Graphic established on the 54th day of observation of a case of pernicious anemia at the apparent recovery.

by the measurements themselves, and the numbering of the 300 erythrocytes. A scheme has been given here only to make the explanation clearer. The same indexes (angle P, angle G, and the total angle) may be established for the reticulocytes. In this case the measurements are made on 100 reticulocytes. The values of these indexes are more outstanding for the reticulocytes than for the erythrocytes, in view of the fact that often even the angle G becomes obtuse. In this case the tangent is calculated on the supplementary angle and its value is negative.

**Application.** In order to demonstrate better the usefulness that the new anisocytic indexes determine, we add here the example of a classical pernicious anemia studied during the crisis on the 2d and 5th day of observation (1,720,000 R.B.C., megalocytosis, Plummer Vinson syndrome) as well as on the 12th day, during a microcytic crisis which determined the use of the liver extract treatment. A response to this treatment was demonstrated as early as the 16th and 21st days, while the 54th day corresponded with complete recovery from the attack (4,800,000 R.B.C.).

In the case of pernicious anemia that we have chosen as an example the figures are very striking. The improvement is manifested at the same time as (P + G) diminishes on the 16th day,

*i. e.*, 4 days after the beginning of the treatment. The recovery is complete on the 54th day with a slight angle G for the erythrocytes, while the reticulocytes are too rare to allow a determination.

TABLE 1.—ANISOCYTOSIS VALUES IN A CASE OF PERNICIOUS ANEMIA.

Day.	Size.	Micro.	Normo.	Macro- cytic.	Tg. P.	Tg. G.	Angle P.	Angle G.
2d	Eryth.	(4.8) 15%	(7.4) 82%	(9.8) 3%	0.38	0.3	21°	17°
	Retic.	(4.5) 8%	(7.5) 32%	(9.5) 60%	1.26	-0.71	52°	145°
5th	Eryth.	(4.6) 17%	(7.7) 68%	(9.3) 15%	0.6	0.3	31°	17°
	Retic.	(4.4) 3%	(7.5) 41%	(9.8) 56%	0.84	-1.53	40°	123°
12th	Eryth.	(4.3) 44.5%	(7.2) 45.6%	(9.4) 9.6%	26.00	0.61	88°	31°
	Retic.	(4.0) 22%	(7.5) 30%	(10.0) 48%	4.1	-1.38	76°	123°
16th	Eryth.	(4.4) 6%	(7.6) 70%	(9.7) 24%	0.5	0.45	27°	24°
	Retic.	(5.4) 3%	(7.7) 71.4%	(9.7) 25.6%	0.33	0.43	18°	23°
21st	Eryth.	(4.8) 19.3%	(7.2) 71.5%	(9.0) 9.3%	0.45	0.28	24°	16°
	Retic.	(5.0) 8%	(6.9) 76%	(9.2) 16%	0.27	0.38	15°	21°
54th	Eryth.	0	(7.7) 85%	(9.2) 15%	0	0.21	0°	12°

The numbers in parentheses above the numbers indicating the percentages express the average diameters of the three groups.

The quantitative value of the anisocytosis is expressed by the total of the angles P and G.

	2d day.	5th day.	12th day.	16th day.	21st day.	54th day.
Erythrocytes . .	38°	48°	119°	51°	40°	12°
Reticulocytes . .	197°	163°	199°	41°	36°	0°

**Summary.** 1. Three new hematologic indexes are introduced which by the simple calculation of the diameters of the blood cells and the recording of the latter in three groups according to their size, allow a numerical value to be given to anisocytosis.

The tangents P and G and the angles P and G demonstrate the qualitative value (micro- and macrocytic) of anisocytosis. The sum of the tangents or angles P and G represent the quantitative value of the same. The latter index goes down at the same time as anisocytosis lessens and approaches 0° in the normal blood.

2. The same indexes may be established on 100 reticulocytes. These obtained are still more outstanding than those for the erythrocytes.

## THE INHIBITING EFFECT OF SNAKE BLOODS UPON THE HEMORRHAGIC ACTION OF VIPER VENOMS ON MICE.

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PREVIOUS investigators have established the fact that venomous snakes are not susceptible to large amounts of their own or closely related venoms. This observation led to the inquiry as to whether any protection was afforded by snake blood against the action of snake-venom. It was ascertained by direct experimentation that snake blood itself when injected into a warm-blooded animal was toxic, causing death after a period of increasing weakness terminating with convulsions. This finding confirmed the work of previous writers.<sup>1,2,4a,5</sup> These experiments, however, have led to the additional observation of a phenomenon, which it is believed has not as yet been described. It consists in the inhibition of the hemorrhage-producing action of pit-viper venoms, when a mixture of the latter and snake blood is injected.

**Methods.** The animals used were white mice weighing approximately 15 gm. each. The venoms used were those from rattlesnake (*crotalus adamanteus*), cotton-mouth moccasin (*agkistrodon piscivorus*), and fer de lance (*bothrops atrox*). Rattlesnake venom (the richest in hemorrhagin factor) was extracted at the laboratory from several snakes and pooled. It was dried immediately and used only on the same day as dissolved. The concentration of the venom dissolved in physiologic saline was 1/1000 (1 mg. of venom in 1 cc. of saline). The venoms of the moccasin and fer de lance were procured from snake farms in a dry form, and used on the same day as dissolved. The blood of snakes was obtained by decapitation and allowing the blood to run into a beaker. The bloods of the rattlesnake and of the non-venomous king snake (*lampropeltis getulus getulus*) were used. In the case of the rattlesnake, the mouth was first taped with adhesive plaster to exclude the possibility of any admixture of venom with the blood. Where plasma was used, the blood was mixed with 3.8% sodium citrate, 1 part to 9 parts of blood; where serum was employed, the blood was defibrinated by shaking with glass beads. In both instances, the blood cells were discarded after separation by centrifugalization. Plasma and serum while standing were kept in refrigeration. Some of the bloods were dried as soon as obtained by freezing-high vacuum apparatus; and when ready for use, dissolved in physiologic saline in the same volume as the original bloods.

Due to significant variations in the individual resistance of mice toward rattlesnake venom, a definite minimal lethal dose could not be established; however, 0.25 mg. of the venom injected subcutaneously was found to be close to a lethal dose for mice in 1 to 2 hours.

Rapid lethal action was insured by the subcutaneous injection of 0.5 mg. Autopsies were performed by stripping the skin from the trunk and by opening the peritoneal cavity, and observing the degree of hemorrhage. All mice injected subcutaneously with venom alone showed intense and extensive hemorrhage throughout the subcutaneous tissues, while those injected intraperitoneally with venom exhibited the same intense hemorrhagic reaction in the serosa. The degrees of hemorrhage found in the tabulated experiments are indicated by the following symbols:

- ++++ = very widespread hemorrhage
- +++ = much less extensive hemorrhage
- ++ = moderate hemorrhage (about 2 sq. cm. in area)
- +
- 0 = no hemorrhage or minute hemorrhage at site of needle puncture

**Experiments.** The first experiments showed that both the blood of the king snake (a non-venomous snake) and the blood of the rattlesnake are toxic. Certain lethal dosages in both cases are 1 cc. when injected subcutaneously and 0.25 cc. when injected intraperitoneally. King snake plasma is the more toxic of the two, requiring smaller doses to produce death. Even when heated at 56° C. for  $\frac{1}{2}$  hour these bloods retain a great portion of their toxicity. Autopsies upon mice so injected revealed an absence of hemorrhages, thereby differing from those autopsied after an injection of venom alone.

Varying amounts of king snake and rattlesnake bloods individually were mixed with rattlesnake venom and injected, subcutaneously and intraperitoneally. In all the mice so injected, death resulted and autopsy showed that there was either an absence, or slight to moderate degree of hemorrhage, whereas those injected with venom alone displayed an intense and very widespread hemorrhagic reaction.

It was further noted that the age of the blood (*i. e.*, the time that it has been kept outside the body) played an important rôle in the degree of inhibition of the hemorrhagic factor of the venom. The blood was much more effective in its control of hemorrhages when it was allowed to stand 24 to 48 hours before using. Blood 2 days old was more protective against hemorrhage from venom than that 1 day old. Fresh blood and old blood (more than 4 days old) had a considerable lesser anti-hemorrhagic effect. Fresh plasma and serum, dried at once by freezing-high vacuum apparatus and then dissolved, after a few weeks, in saline in the same proportion as the original plasma or serum, appeared to retain its anti-hemorrhagic property, unless kept standing in solution for more than 2 days. Both heated king snake and rattlesnake bloods (heated to 56° C. for  $\frac{1}{2}$  hour) still possessed most of their protective properties against the hemorrhagic action of rattlesnake venom. It must be borne in mind that the bloods of individual snakes vary as to their physiologic effects. Some are more toxic than others; and some appear to have more of an anti-hemorrhagic factor. The presence of a lesser amount

of this anti-hemorrhagic factor in some snake bloods may account for some apparently conflicting results. It may safely be assumed, however, that all of these bloods have some protection against the hemorrhages produced by venoms. The variation is minimal when 2-day-old blood is used. Table 1 summarizes these results.

The blood and venom need not necessarily be injected together. It was found when venom was injected within one hour after the administration of plasma or serum that there was still inhibition of hemorrhages, but to a lesser degree.

The anti-hemorrhagic factor of rattlesnake blood is active not only against rattlesnake venom but also operates against the hemorrhagic action of other venoms, those of the moccasin and the fer de lance (Table 2).

The anti-hemorrhagic principle present in snake blood was not found in the sera of various warm-blooded animals (Table 3).

**Comment.** These experiments show that snake blood inhibits the hemorrhagic action of snake venom, without affecting the lethal factor. Whether the resultant death is caused by the toxins of the venom other than hemorrhagin, or by the toxic action of the snake blood, or by the combination of the two, has as yet not been determined. Phisalix and Bertrand<sup>3,4b</sup> believed that death was produced by the toxic substances in snake blood, which existed side-by-side with antitoxins. They stated that by heating the blood to 58° C. for 15 minutes these toxins were destroyed, but the antitoxic activity was preserved. However, the experiments showed that heated snake blood (56° C. for 30 minutes) retained its toxicity, contrary to the findings of Phisalix and Bertrand. It is possible that a complete neutralization may have occurred and that the resultant death was mainly caused by the toxins of snake blood.

The action of snake blood is quite different from immune serum containing antivenin. Antivenin,\* a true antitoxin, protects not only against the hemorrhagin of snake venom but also against the death of the animal. One might suspect that the hemorrhage-protecting power of snake blood in these experiments could be explained by the presence of specific antibodies prevailing in the blood stream, with death the result of the toxic action of foreign blood proteins. However, the following points seem to indicate that this phenomenon is not that of a specific antibody reaction, but rather the result of a non-specific neutralization of venom hemorrhagins:

1. Since auto-antibodies have been observed only under very exceptional conditions (as in paroxysmal hemoglobinuria), it is very doubtful that the anti-hemorrhagic effect of rattlesnake serum against its own and homologous venoms is due to a specific antibody.
2. Immune sera (antivenins) against snake venoms are specific for the venoms for which they have been prepared; whereas, as far

\* The antivenin, a polyvalent serum, for nearctic *Crotalidae* was obtained through the courtesy of Mulford Biological Laboratories, Philadelphia, Pa.

TABLE 1.—THE RESULTS OF INJECTIONS OF VENOM ALONE AND THE INJECTIONS OF MIXTURES OF VENOM AND SNAKE BLOOD.

Type of snake blood.	Amt., cc.	Crotalus adaman- teus venom, mg.	Admin.	Time of death.	Degree of hem.	Remarks.
0	0	$\frac{1}{2}$	s	20'-1 hr.	++++	Control
0	0	$\frac{1}{2}$	p	15'	++++	Control
0	0	$\frac{1}{2}$	s	1-2 hrs.	++++	Control
0	0	$\frac{1}{2}$	s	Lived	....	Control
Fresh R.S.S. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	a	2-2½ hr.	++++	Blood with- drawn from heart showed no hemolysis
Fresh R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	1½-2 hr.	++++	
Fresh R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	2-3 hr.	some ++	
Fresh R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	½-3 hr.	some ++	
Fresh R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1-2½ hr.	some ++	
Fresh R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	6 hr.	some ++	
1-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	2½ hr.	++	
1-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	½-2½ hr.	sev. 0 occ. ++	
1-day-old R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1½ hr.	0	
1-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1½ hr.	0	
1-day-old K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	p	20'	0	Venom injected ½ hr. after plasma.
1-day-old K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	½ hr.	0	
1-day-old K.S.P. . . . .	1	$\frac{1}{2}$	s	1½ hr.	0	
1-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	2½ hr.	+	
1-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	1 hr.	+	
1-day-old R.S.P. . . . .	$\frac{1}{4}$	$\frac{1}{2}$	s	½-1 hr.	0	
1-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1 hr.	0	
2-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	½-1 hr.	some +	
2-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1-2 hr.	some ++	
2-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	p	½-6 hr.	most 0 occ. +	
2-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	½-1½ hr.	most 0 occ. +	
2-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	p	½ hr.	0	
2-day-old K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1-4 hr.	most 0 or +	
2-day-old heated K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1½-5 hr.	occ. ++ most 0	
2-day-old heated K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	p	1 hr.	occ. + 0	
3-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	2 hr.	0	
3-day-old R.S.P. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	Lived	0	
3-day-old R.S.P. . . . .	$\frac{1}{4}$	$\frac{1}{2}$	s	½-6 hr.	0	
3-day-old R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	3 hr.	0	
4-day-old heated R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	2½ hr.	+	
6-day-old R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	1 hr.	+	
9-day-old heated K.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	4½ hr.	+++	
Freshly dried R.S.S. . . . .	$\frac{1}{16}$	$\frac{1}{2}$	s	1½ hr.	++	Used same day as dissolved.
Freshly dried R.S.S. . . . .	$\frac{1}{4}$	$\frac{1}{2}$	s	15'	0	
Freshly dried R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s		0	
Freshly dried R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	2½ hr.	+	Used 1 day after dissolved
Freshly dried R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	20'	+	
Freshly dried R.S.S. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	½ hr.	++	Used 4 days after dissolved
Freshly dried R.S.P. . . . .	$\frac{1}{2}$	$\frac{1}{2}$	s	40'	++	

Abbreviations: R.S. = rattlesnake, K.S. = king snake, P = plasma, s = subcutaneous, p = peritoneal, S. = serum, hem. = hemorrhage.

All heated bloods were heated to 56° C. for ½ hour.

All dried bloods were dried on the same day as collected. They were kept in dry form for a few weeks and then dissolved and used after the periods of time indicated in the table.



as our findings go, snake sera protect against the hemorrhagic action of heterologous venoms. This observation can be reconciled with the assumption of specificity only by postulating a multiplicity of antitoxins in snake sera.

TABLE 2.—THE PROTECTIVE ACTION OF RATTLESNAKE PLASMA (R.S.P.) AGAINST THE HEMORRHAGIC ACTION OF OTHER VIPER VENOMS.

Amount of R.S.P.	Venom used.	Venom in mg.	Degree of hemorrhage.
0	<i>Bothrops atrox</i> . . . . .	$\frac{1}{2}$	++++
0	<i>Agkistrodon piscivorus</i> . . . . .	$\frac{1}{2}$	++++
$\frac{1}{4}$ cc. (2-day-old)	<i>Bothrops atrox</i> . . . . .	$\frac{1}{2}$	0
$\frac{1}{4}$ cc. (2-day-old)	<i>Agkistrodon piscivorus</i> . . . . .	$\frac{1}{2}$	0

Plasma and venom mixed immediately before subcutaneous injection.

All mice were killed and autopsied after 1 hour and 45 minutes.

3. Fresh snake plasma or serum is not as effective in its inhibition of hemorrhagic activity as is blood aged from 1 to 4 days, and rapidly loses this power. This would be an unusual finding for a specific antibody, although it does not exclude it.

TABLE 3.—THE LACK OF PROTECTIVE POWER OF VARIOUS BLOODS OF WARM-BLOODED ANIMALS AGAINST THE HEMORRHAGIC ACTION OF RATTLESNAKE VENOM.

Type of blood and amount in cc.	<i>Crotalus adamanteus</i> venom, mg.	Time of death, hrs.	Degree of hemorrhage.
Rabbit serum (2-day-old) . . . . .	$\frac{1}{2}$	2	++++
Fresh human plasma . . . . .	$\frac{1}{2}$	$1\frac{1}{2}$	++++
Human plasma (3-day-old) . . . . .	$\frac{1}{2}$	$1\frac{1}{2}$	++++
Guinea pig serum (1-day-old) . . . . .	$\frac{1}{2}$	$1\frac{1}{2}$	++++
Horse serum (age unknown) . . . . .	$\frac{1}{2}$	1	++++

Mixtures of blood and venom injected subcutaneously in mice.

**Conclusions.** 1. King snake and rattlesnake bloods protect against the hemorrhagic action of viper venoms, but do not prevent death.

2. The time that the snake blood has been kept outside the body plays an important rôle in its power to inhibit the hemorrhages caused by viper venoms.

3. The bloods of mammals are not protective against the hemorrhagic action of rattlesnake venom.

4. Evidence is cited supporting the idea that the action of snake blood in protecting against the hemorrhages produced by viper venoms is not identical to that afforded by antitoxin (antivenin).

5. The toxic and anti-hemorrhagic properties of snake blood are thermostabile, retaining them after heating to 56° C. for  $\frac{1}{2}$  hour.

6. Blood, both from venomous and non-venomous snakes, is toxic; but the resultant death, unlike that produced by viper venoms is not accompanied by hemorrhages.

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## THE SIGNIFICANCE OF THE OXIDATION OF SULPHANILAMIDE DURING THERAPY.\*

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THE detection of methemoglobin in the blood of patients treated with sulphanilamide<sup>1,2,7,10,12,18,19,26</sup> provides an important clue to the possible mechanism of action of the drug.<sup>24</sup> Since this abnormal pigment is formed from hemoglobin only by the action of strong oxidizing agents,<sup>8</sup> the opinion seems warranted that a rather powerful oxidizing agent is present during therapy. Sulphanilamide itself is not an oxidant and does not form methemoglobin outside the body.† It follows, therefore, that administration of the drug is accompanied by the constant formation of some substance capable of oxidizing hemoglobin to methemoglobin.

The problem; then, is whether such a substance can be formed from sulphanilamide. This may readily be accomplished<sup>25</sup> by exposing the drug‡ to the rays of an ordinary ultraviolet lamp in the presence of oxygen. Oxidation of sulphanilamide occurs in a minute or two.<sup>13</sup> The resulting violet blue solution, which probably contains several products, oxidizes hemoglobin to methemoglobin instantly.<sup>12</sup> During this second oxidation, the blue oxidizing solution turns brown. It is obviously important to know whether this brown pigment exists in sulphanilamide-treated patients' blood, indicating the occurrence *in vivo* of these oxidations. Evidence on this point has been difficult to obtain. However, by using the Hardy recording spectrophotometer§ at the Massachusetts Institute of Technology, we have shown that the blood of these patients contains a colored substance with spectral characteristics similar to those of the brown pigment formed when the blue photo-oxidation product oxidizes hemoglobin to methemoglobin *in vitro*.<sup>12</sup>

Additional evidence for the *in vivo* oxidation of sulphanilamide has come recently from Rosenthal's<sup>27</sup> observation that 1 to 3% of an oxidation product of the drug appears in the urine of sulphanilamide-treated patients.

Experimentally, there are many observations which indicate that when bacterial growth is suppressed by sulphanilamide, the

\* Read at the Third International Congress for Microbiology, September 4, 1939.

† Unpublished experiments.

‡ The sulphanilamide is dissolved in water or dilute buffer (pH 7.3) in the optimal therapeutic concentration 10 mg. per 100 cc. or 1 to 10,000 and exposed in a thin layer in an open vessel.

§ Designed by Prof. A. C. Hardy,<sup>16</sup> this accurate, automatic machine utilizing photoelectric cells draws a smooth curve of the light transmitted through a sample from 400 to 700  $\mu$ .

drug itself is oxidized. Comparative studies of the growth of virulent  $\beta$  hemolytic streptococci in the presence and absence of sulph-anilamide were made with Janeway.\*<sup>4,14</sup> Chart 1 (Chandler and Janeway<sup>4</sup>) shows growth curves, with plate counts taken at 2-hour intervals, of cultures of  $\beta$  hemolytic streptococci with and without 10 mg. per 100 cc. sulphanilamide. It is striking that during the first 4 or 5 hours of growth, the sulphanilamide culture grows equally with the control. In other words, although the drug is in solution and is readily diffusible, no bacteriostasis occurs until the bacteria are in

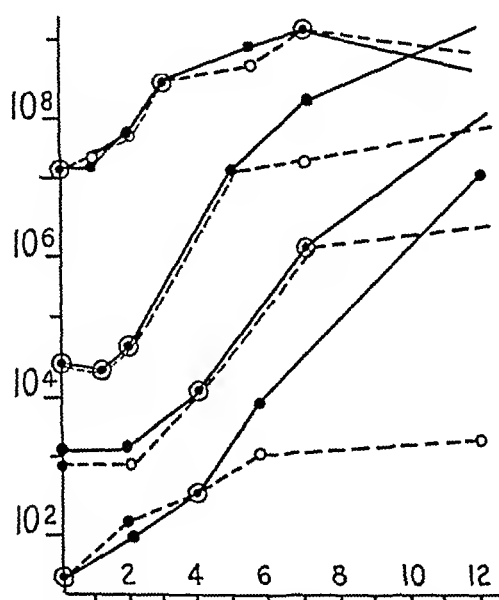


CHART 1.—EFFECT OF SULPHANILAMIDE ON GROWTH OF HEMOLYTIC STREPTOCOCCI IN VITRO.

Ordinate—logarithm of number of bacteria present. Abseissa—time in hours. Broken line represents medium with 10 mg. per 100 cc. sulphanilamide, solid line represents control medium without sulphanilamide. No bacteriostasis manifest during first 4 to 5 hours until logarithmic phase. Larger inocula give less or no bacteriostasis.

the logarithmic phase of rapid growth. If the assumption be made that the bacteria oxidize the drug to the potent oxidant, then by analogy with Dubos' experiments,<sup>9b</sup> vigorous oxidation would proceed only after the bacteria had entered the logarithmic phase of growth. That this actually occurs is fairly clear. Using bright platinum electrodes and a potentiometer, Warren<sup>31</sup> and the writer working independently<sup>14</sup> found an elevated oxidizing electrode potential in hemolytic streptococcus cultures containing sulphanilamide during the logarithmic period (Chart 2A). This elevation was maintained in cultures containing the drug, whereas in control cultures the usual reducing conditions marked by falling potentials

\* Some experiments reported in Ref. 14, others to be published with Janeway.

prevailed.<sup>3,15</sup> These results suggested the formation of an oxidant in the sulphanilamide media. Furthermore, since oxidation of sulphanilamide to a strong oxidant requires the participation of oxygen,<sup>13</sup> removal of oxygen at the beginning of the experiment should prevent this chemical change and coincidentally, prevent bacteriostasis. This is in fact the case. With six strains of Group A hemolytic streptococci,<sup>30</sup> if removal of oxygen and reduction are complete *before* inoculation,\* bacteriostasis by sulphanilamide is prevented.†

The assumption that oxidizing conditions are necessary for bacteriostasis is further supported by the low threshold of inoculum size. While increasing sulphanilamide effect with decreasing inocula is a predictable occurrence (as Chart 1 shows), when the relatively low inoculum limit of 100,000 organisms per cc. is exceeded no bacteriostasis can be detected, even with a large excess of sulphanilamide. Potentiometric comparison (Chart 2B) of the electrode behavior of small and large inocula shows that whereas the small inoculum permits longer maintenance of the elevated oxidizing potential, the large inoculum rapidly establishes reducing conditions inimical to oxidative reactions and oxidants.<sup>14</sup> In other words, there seem to be two antagonistic reactions: (a) the creation from sulphanilamide of an oxidant and its successful functioning; (b) the establishment of reducing conditions in the media by the metabolic activity of the bacteria. As the size of the inoculum is increased, reducing conditions prevail sooner and either greatly inhibit the oxidation of sulphanilamide or interfere with the oxidation reactions of the newly formed oxidant. Accordingly, it is evident that bacteriostasis can occur only when oxidizing conditions prevail over reducing conditions.

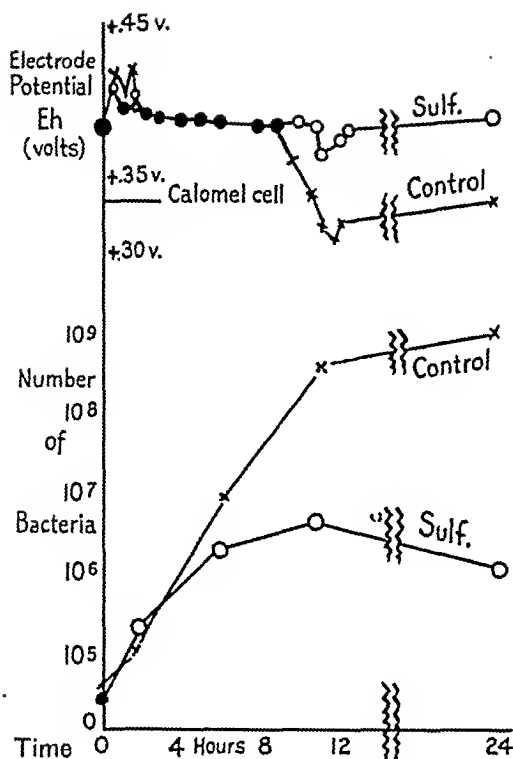
A parallel may be drawn from the clinical experience that sulphanilamide rapidly controls cases of septicemia, infections which take place in a well oxygenated environment, whereas it fails to show much effect against infections with similar organisms in closed cavities or abscesses where oxygen lack and intense reducing conditions prevail. Other factors may also play a rôle as Lockwood has pointed out.<sup>22</sup>

If this view is correct, it ought to be possible to augment the effect of the drug by favoring oxidation and by preventing reduction. As a matter of fact, simple aeration of the culture by agitation augments bacteriostasis. The next logical step is to preform an

\* Technically this object cannot be accomplished by using the various types of hydrogen anaërobic jars, which will remove oxygen in the superambient atmosphere of the jar but fail to effect reduction of the media and bring about complete removal of oxygen before any sulphanilamide has been oxidized. Types 1, 6, 14, 18 and two strains that could not be typed were tested in 0.01% dextrose infusion broth or 20% horse serum neopeptone water. In the former, medium spontaneous reduction under vaseline sufficed; in the latter, it was necessary to add 0.1% neutralized cysteine<sup>14</sup> for complete reduction of the methylene blue oxygen indicator.

† Some experiments reported in Ref. 14, others to be published with Janeway.

2 A



2 B

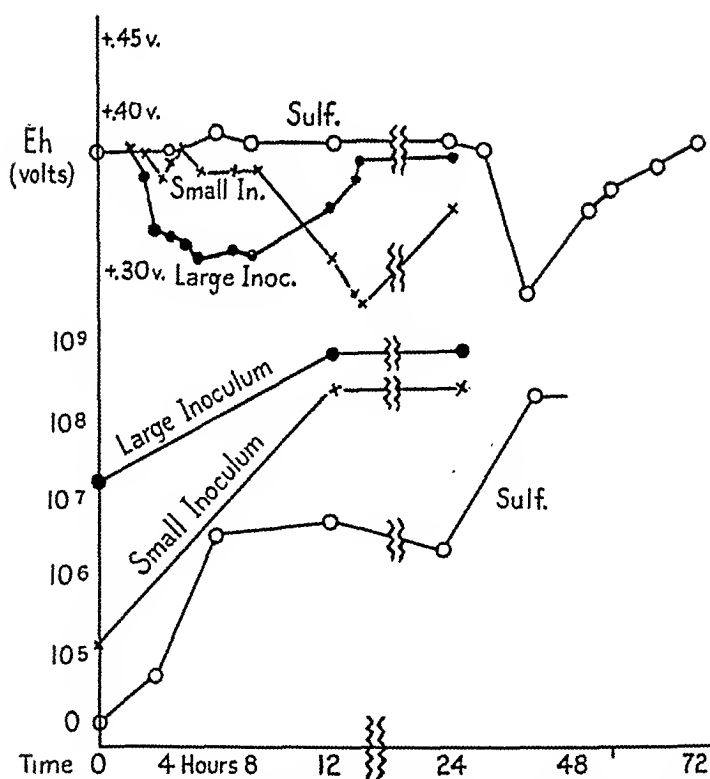
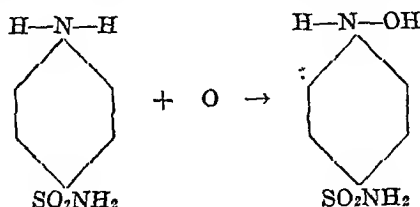


CHART 2.—CHANGES IN THE ELECTRODE POTENTIAL OF CULTURES OF HEMOLYTIC STREPTOCOCCI RESULTING FROM ACTION OF SULPHANILAMIDE.

Upper curves show electrode potential variations in control and sulphanilamide containing cultures. Lower curves show growth rate of these cultures. Electrode potential in sulphanilamide containing culture elevated during bacteriostasis while potential of control fell. When the sulphanilamide containing cultures finally grew out (Chart 2B) then the potential there also fell. Rapid fall of electrode potential in culture with large inoculum; delayed fall with small inoculum.

oxidant from the drug before use. This has been accomplished by Drs. Rosenthal and Bauer in Washington who very kindly supplied me with a sample. The first oxidation product of sulph-anilamide is 4-hydroxylamino benzene sulphonamide, an unstable compound formed by introducing an atom of oxygen into the amino group without loss of hydrogen.\* Like the photooxidation product†



of sulphanilamide, this sample of hydroxylamino sulphonamide oxidizes hemoglobin to methemoglobin and inactivates catalase. Hydroxylamino sulphonamide accomplishes immediate bacteriostasis, thereby completely eliminating the previously described initial growth period (Table 1). Furthermore, it gives more prolonged bacteriostasis possibly because there is more of the oxidant.

TABLE 1.—BACTERIOSTASIS WITH 4-HYDROXYLAMINO SULPHONAMIDE.

Interval.	Bacterial counts—colonies in thousands per cc.					
	Initial inoculum.	2 hrs.	4 hrs.	6 hrs.	8½ hrs.	18 hrs.
Control . . . . .	86	340	5700	..	350,000	++++
Sulphanilamide* . .	86	440	5450	..	32,500	++++
Hydroxylamino sulphonamide* .	86	117	1000	..	25,000	++++
Control . . . . .	15	150	1000	25,000	86,000	++++
Sulphanilamide* . .	15	140	1300	6,000	21,000	++++
Hydroxylamino sulphonamide* .	15	7	100	100	1,000	++++

\* 10 mg. per 100 cc. in 0.1% dextrose beef heart broth. Strain: Group A hemolytic streptococcus H (Gay). Medium: 0.1% dextrose beef heart broth.

Recently, utilizing empyema fluid drawn and maintained under seal, it has been possible to demonstrate the marked bacteriostatic action of 4-hydroxylamino benzene sulphonamide in this physiological reducing anærobic environment where both sulphanilamide and sulphapyridine failed to elicit any bacteriostatic action.

At this point several questions arise. Has an oxidation product of sulphanilamide, or a diminution of sulphanilamide concentration, been detected chemically in cultures? (See addendum.) Special methods would be needed to detect hydroxylamino-sulphonamide under such conditions (see addendum). This substance is very

\* *In vivo* or *in vitro* oxidation to the free radical by loss of an electron or loss of hydrogen may occur. This, too, would be an unstable, powerful oxidizing agent.

† This blue product has not been shown to be bacteriostatic probably because it is formed only in dilute solution and is rapidly reduced when added to media.<sup>13</sup>

unstable and it is unlikely that significant amounts of it could be present at any one time. Furthermore, estimations by the Marshall method<sup>23</sup> do not distinguish between sulphanilamide and the oxidant. The characteristic lability that interferes with the demonstration of such a substance during therapy may, however, be a very valuable attribute. Thus, instability of the oxidant might provide for a gentle throttling of bacteria rather than wholesale slaughter of both host cells and hostile cells. It might produce fractional rather than total methemoglobinemia.

The transitory existence and rapid destruction of such a substance in the test tube is supported by the following facts:<sup>4</sup> (a) sulphanilamide containing media in which bacteriostasis has occurred and in

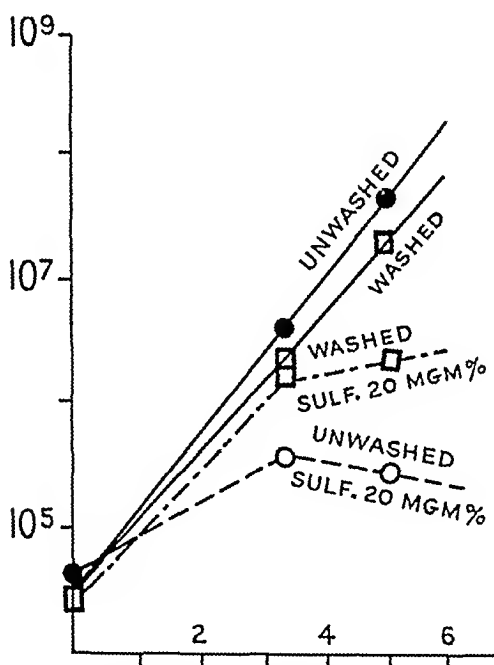


CHART 3.—ALTERATION OF HEMOLYTIC STREPTOCOCCI CAUSED BY SULPHANILAMIDE REVERSED BY WASHING.

Bacteria previously grown in media containing sulphanilamide show prompt bacteriostasis on subculture in sulphanilamide containing media (broken line). Washing reduces this effect, and subculture in sulphanilamide-free media (solid line) shows no bacteriostasis at all.

which the oxidant is presumably present, when freed of their bacteria, are no more bacteriostatic than fresh sulphanilamide media; (b) an inoculum composed of bacteria obtained from such sulphanilamide containing media during bacteriostasis, on subculture in fresh sulphanilamide media responds at once to the drug without the usual initial growth period; but (c) on subculture in sulphanilamide-free media, such bacteria grow entirely normally, showing no

sign of their erstwhile disability. On the other hand (*d*), if sulphanilamide-grown organisms are washed, they behave like ordinary bacteria in fresh sulphanilamide media, indicating at best only a loose binding between bacteria and the oxidant. Apparently this oxidation proceeds along with the normal bacterial metabolic oxidations at the surface of the bacteria, so that the oxidant formed may survive only long enough to function. The bacteria grown in sulphanilamide-containing media are reversibly altered and this reversal is prevented only by the continued action of sulphanilamide, which would seem to keep the reaction going to the right against a tendency toward reversal to the left (see Chart 3).

It is also of considerable importance that certain tissues aerobically induce the conversion of sulphanilamide to a methemoglobin-producing oxidant, as shown recently by Harris<sup>17</sup> with surviving liver or kidney tissue *in vitro* (see addendum). It should be emphasized that only a particular oxidation of sulphanilamide is effective: that in which the product formed is itself an oxidizing agent. This means that inactive sulphanilamide is transformed into a highly active agent by chemical legerdemain. If human tissues can transform sulphanilamide into the effective agent in the absence of infection, a rational basis exists for the use of sulphanilamide to forestall streptococcal infections as described by Coburn.<sup>6</sup>

Now of what use is an oxidant? How may an oxidant inhibit bacterial propagation? These questions were answered long before the advent of sulphanilamide. Dubos clearly showed that oxidized substances inhibited growth and that reduction of these same substances favored growth.<sup>9a</sup> Fildes demonstrated that the same conditions governed the growth of anaerobes,<sup>11</sup> and Kligler and Guggenheim induced anaerobes to grow in the presence of oxygen by lowering the potential of the media.<sup>21</sup> Schmelkes,<sup>28</sup> and later Clark,<sup>5</sup> showed that the usual inhibitory halogen oxidizing compounds, even in large quantities, were ineffective provided the usual electrode potential of the bacterial cells was not elevated. The mechanisms involved have been elucidated by the studies of Clark and Hellerman<sup>20,29</sup> on isolated systems: enzymes such as papain, cathepsin and urease, and bacterial toxins and hemolysins are reversibly inactivated by oxidants and may be reactivated by reductants. The application of these facts to the present problem is that sulphanilamide bacteriostasis may rest upon the production of oxidizing conditions which serve to inactivate enzymes and inhibit bacterial growth; that sulphanilamide bacteriostasis is nullified by reducing conditions which reactivate enzymes and favor bacterial growth.

\* Discussion by author at Am. Med. Assn. meeting, May, 1939, section on Pharmacy and Therapeutics (to be published).



**Summary and Conclusions.** The conclusion that sulphanilamide is oxidized during therapy is supported by these observations:

1. Complete, initial deprivation of  $O_2$  interferes with bacteriostasis.

2. Increased oxygen availability magnifies bacteriostasis.

3. Reducing agents and large inocula, which rapidly reduce the potential, obliterate bacteriostasis despite excess of sulphanilamide.

4. The use of a preformed oxidant derived from sulphanilamide, 4-hydroxylamino sulphonamide,\* eliminates the usual initial growth period before bacteriostasis appears and gives a more prolonged effect than sulphanilamide.

5. The occurrence of methemoglobinemia during therapy and the occurrence of an oxidation product\* of sulphanilamide in the urine of treated patients confirm the view that an oxidant is produced in the blood or tissues of the patient.

\* *Addendum.* This has since been similarly detected in a sulphanilamide-containing bacterial culture, in the product formed by ultraviolet irradiation of sulphanilamide and in the methemoglobin-forming oxidant produced by surviving liver and kidney tissue oxidation of sulphanilamide. The product of ultra-violet irradiation is significantly different from these in giving a positive Rosenthal test after treatment with alkali. Alkali decomposes 4-hydroxylamino sulphonamide which subsequently fails to show this test. A detailed report will be published separately on this point.

The writer wishes to express his gratitude to Dr. Hans Zinsser, of the Harvard Medical School, and to Prof. George S. Forbes, of the Harvard Chemical Laboratory, for their hospitality and encouragement while this work was in progress in their laboratories. To Drs. Reuben Ottenberg and Charles A. Janeway are due thanks for invaluable criticism and suggestions.

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## SCARLET FEVER THERAPY.

## A COMPARISON OF CONVALESCENT SERUM AND SULPHANILAMIDE.

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THE object of this study is an attempt to compare the results following the use of human convalescent scarlet fever serum in the treatment of scarlet fever with those following the use of sulphani-  
lamide. We have found, as have others, that when convalescent  
scarlet fever serum is given early in the disease in adequate amounts,  
there is an apparent decrease in the mortality rate, as well as a  
reduction in the complications. As a rule, all the symptoms im-  
prove, and there is a reduction in the length of time until the  
temperature reaches normal.<sup>2</sup>

Recently, the value of sulphanilamide in the treatment of scarlet  
fever has been studied by Wesselhoeft and Smith,<sup>14</sup> Peters and  
Harvard,<sup>8</sup> Schwentker and Waghelstein,<sup>11</sup> Sako, Dwan and Platou,<sup>10</sup>  
Hoyne and Bailey,<sup>5</sup> Hogarth,<sup>4</sup> Place,<sup>9</sup> and Strom.<sup>12</sup>

We have studied 300 hospital cases of scarlet fever, divided into  
groups of 100 each. The first group (A) received non-specific ther-  
apy and general care. The case types were ordinary in character  
and would be classified as mild. The cases in the second group (B)  
were mild or moderately ill and were given neoprontosil (Winthrop-  
Brand of Azosulfamide, Disodium 4-sulfamide-phenyl-2-azo-7-  
acetyl-amino-1-hydroxynaphthalene 3, 6-disulfonate). Patients in  
the third group (C) which were selected for convalescent serum  
therapy were moderately or severely ill. In each group the cases  
were divided into 5-year age periods up to the age of 20. All  
cases occurred during the same period of time, January, February,  
March and April of 1939. All were attended by the same profes-  
sional personnel.

**Method.** Patients under 5 years of age were given 10 gr. of neoprontosil  
twice daily for 3 days. The following 4 days they were given 10 gr. once  
daily. From the 16th to the 23d day, 10 grains again were given daily.  
Those over 5 years of age were given 10 gr. 3 times daily for the first 3 days.  
The next 4 days 10 gr. twice a day. From the 16th to the 23d day, they  
were given 10 gr. twice daily. The medication was given 1 hour before  
meals, and was accompanied by soda bicarbonate. The second course of  
neoprontosil, beginning on the 16th day, was given to cover the third week  
complications which are apt to occur. The method of preparing and using  
convalescent scarlet fever serum has been described in a previous article.<sup>3</sup>

The control cases were admitted to the hospital somewhat later than were the cases in the other groups (see chart). In the serum-treated cases the temperature reached normal in a shorter length of time (1.7 days) than in the control (2.8 days).

TABLE 1.—COMPARISON OF NEOPRONTOSIL AND CONVALESCENT SCARLET FEVER SERUM IN THE TREATMENT OF SCARLET FEVER.

Ages.	A. Control (mild).						B. Serum (mod. and severe).						C. Neoprontosil (mod.).					
	0-5.	5-10.	10-15.	15-20.	20.	T.	0-5.	5-10.	10-15.	15-20.	20.	T.	0-5.	5-10.	10-15.	15-20.	20.	T.
Number of cases . . .	18	56	18	3	5	100	7	32	15	14	32	100	12	41	17	6	24	100
Mean day of disease on admission . . .	3	4	3.7	3.3	5.5	3.9	2	4.6	3	3	3	3.1	2.8	2.9	2.2	6	2.6	3.3
Mean duration of pyrexia after admission	3.3	2.5	3	1.6	1.2	2.3	2.5	2	1.2	1.1	1.5	1.7	3.8	4.5	2.9	2.3	3	3.3
Cervical adenitis . . .	6	9	3	..	..	18	1	5	2	..	..	8	4	6	..	1	3	14
Otitis media . . .	4	5	3	..	..	12	2	8	1	..	..	11	..	5	1	1	1	8
Peritonsillar abscess . . .	..	1	..	..	..	1	..	..	1	..	..	1	..	..	..	..	1	1
"Arthritis" (synovitis) . . .	..	..	..	..	..	..	..	1	..	2	1	4	..	1	2	1	2	6
Nephritis . . .	..	2	..	..	..	2	..	..	..	1	..	1	..	2	..	..	..	2
Cellulitis or extremity infections . . .	1	4	..	..	..	5	1	2	..	..	1	4						
Reerudescence . . .	..	1	..	..	..	1	..	..	..	..	..	..	..	1	..	..	1	2
Cases having 1 or more comp. or reerudescence . . .	8	22	3	..	..	33	2	16	4	2	2	26	4	15	3	3	7	32

It took longer for the patients' temperature to reach normal in the neoprontosil cases (3.3 days). A large number of cases between the ages of 5 and 10 occurred in each group. Cervical adenitis occurred 18 times in the control group, 8 times in the serum-treated group, and 14 times in the neoprontosil group. Otitis media occurred 12 times in the control group, 11 times in the serum group, and 8 times in the neoprontosil group. Peritonsillar abscess developed in 1 case of each group. Nephritis occurred once in the serum group, and was found in 2 cases in each of the other two groups. Extremity infections (onychia and paronychia) or cellulitis developed in 5 of the controls and in 4 of the serum group. Arthritis (small bone synovitis) occurring in the first 10 days of the disease was found 4 times in the serum group and 6 times in the neoprontosil group. A reerudescence of the disease was noted in 2 cases of the neoprontosil group and 1 of the control group. The number of cases having complications (reerudescence included) were 26 in the serum-treated group, 32 in the neoprontosil group, and 33 in the control group.

There was noted an appreciable effect on the toxic phase of the disease following the use of convalescent serum. Although these cases were admitted to the hospital earlier in the course of their disease, it will be noticed that there was an earlier disappearance of fever. Amelioration of throat symptoms, and a sense of well-being followed shortly after the use of the serum. Such phenomena were not noted after the neoprontosil or in the control group.

A condition resembling the toxic phase of the disease can be produced through the use of scarlet fever toxin (immunization) in which no bacteria are involved. Neoprontosil, in our experience, has not improved this condition.

McIntosh and Whitby<sup>7</sup> have pointed to the time lag before the drug becomes effective *in vivo* or *vitro* and the tendency to primary stimulation of bacterial growth. This "lag" in action is responsible for the failure of the drug to check the initial local multiplication and invasion of organisms. This lagging period may be sufficiently long to endanger the lives of patients. We have observed 6 instances in which it was thought advisable to withdraw neoprontosil and substitute serum.

**Case Abstracts.** The following 2 cases illustrate this point: **CASE 1.**—On April 17, 1939, Miss A. L., aged 23, developed a severe angina. Three days later a punctiform rash was noted over the entire body and extremities, but was most marked in the folds of the body. A septic fever curve was present. Sulphanilamide (180 gr. daily) had been given for 5 days when she was seen by one of us (M. F.). The patient was comatose and showed evidence of marked dehydration, respiratory difficulty and cyanosis. The temperature was 105°, the pulse rate was 140, the respiratory rate 38. She also presented an extremely congested throat, strawberry tongue, and scarlatiniform rash.

Convalescent scarlet fever serum (40 cc.) was given, followed later by 50 cc. The temperature dropped 4° within 24 hours. On the 3d hospital day, the patient was rational and able to eat her meals, but complained of pain in the right side of her chest. Examination presented evidence of lobar pneumonia, which was treated with sulphapyridine. On the 6th day of the lobar pneumonia, a bloody membranous cast of the trachea was expectorated and following this an uneventful hospital course ensued.

**CASE 2.**—R. M., aged 11, was admitted to the South View Hospital on February 27, 1939. Examination revealed a well-developed and well-nourished white male child, acutely ill, having a temperature of 103.6°, pulse 140, and respiratory rate 20. He presented marked circumoral pallor, injected pharynx and soft palate with a strawberry tongue and a fine scarlatiniform rash over the entire body. Pastia's sign was present.

The patient was given 10 gr. of neoprontosil 3 times daily, but on the 2d day of his hospital stay, the patient still had a septic fever curve and was delirious. It was thought best to discontinue the neoprontosil and give convalescent scarlet fever serum (40 cc.). This caused the patient's temperature to level off rapidly. There was marked clinical improvement and an uneventful convalescence followed.

Colebrook and Kenny,<sup>1</sup> and Long and Bliss<sup>6</sup> found that prontosil had little effect upon infections caused by the hemolytic streptococci of low mouse virulence. Although most of our cases were of moderate severity, we have seen severe early cases not notably improved after massive doses.

The total number of complications was less in the severe cases treated by convalescent serum than either of the other groups consisting of mild and moderate cases. Otitis media occurred less frequently in the neoprontosil group which may have been due to the drug or the milder type of this disease in these cases. A study of a larger number of cases is to be encouraged.<sup>13</sup> No cases of cellulitis or extremity infections occurred after the use of neoprontosil.

We feel, as a result of the above study and from other clinical experiences, that neoprontosil as well as convalescent serum has a place in the treatment of scarlet fever. However, it is not for the toxic phase or type of disease. Four cases of hemolytic blood stream infections occurring in scarlet fever have received the drug and have recovered. Otitis media and mastoiditis appear to have been helped by its administration. Two cases of hemolytic streptococcus meningitis following scarlet fever have been treated successfully by neoprontosil at South View Hospital. We have also noted improvement after its use in deep-seated recesses of infection. Surgical drainage necessarily complements the drug action.

**Conclusion.** Neoprontosil seems to have less effect on the initial toxicity and pyrexia of scarlet fever than does convalescent scarlet fever serum, though both have been found useful in the treatment of this disease.

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#### LIMITATIONS OF THE USE OF DIGITALIS FOR AMBULATORY PATIENTS WITH AURICULAR FIBRILLATION.\*

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It is well recognized clinically that patients with auricular fibrillation who have little or no evidence of heart failure complain of pal-

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pitation, a feeling of discomfort and heart consciousness after exercise or emotional strain and rapid heart rate, even when their ventricular rates at rest may be normal or only slightly elevated. It has been claimed that if adequate doses of digitalis are given to patients with auricular fibrillation, the marked increase in the rate of the ventricles can be prevented (Mackenzie<sup>11</sup>). However, Blumgart<sup>1</sup> as a result of his experiments on ambulatory patients, concluded that digitalis slowed the resting ventricular rate in auricular fibrillation, but failed to protect the ventricles from the exaggerated response to exercise. The results of Boas<sup>2</sup> and Levy and Boas<sup>8</sup> are in accord with Blumgart's. Boas<sup>2</sup> and Boas and Goldschmidt<sup>3</sup> have suggested that patients with auricular fibrillation can be classed into (a) high-strung, nervous individuals with labile ventricular rates and (b) calm and phlegmatic individuals with stable ventricular rates. The latter group are readily kept under control by digitalis, but the former still exhibit exaggerated ventricular responses to exercise and emotional upsets even after thorough digitalization.

The apparent discrepancy between Mackenzie's experience and those of Blumgart and of Boas *et al.* suggested to us the need of reinvestigating this subject more systematically. Eight coöperative patients with auricular fibrillation from the Mandel Clinic were selected for intensive study. In 4 the etiology of the auricular fibrillation was chronic rheumatic heart disease, in 3 it was coronary sclerosis and in 1 it was a combination of the two. All of the patients were ambulatory.

**Method.** The patients were told to continue their habitual régime, and the digitalis medication was controlled. The exercise test employed was standardized for each patient by determining the amount of exercise the patient could tolerate on the Master stairs 3 weeks after digitalis had been stopped. The rate of exercise was the pace set at this time by the patient. The duration of exercise and the number of trips (of 5 steps) was measured. The exercise was terminated when the patient felt uncomfortable either because of palpitation, fatigue or shortness of breath. The same amount and rate of exercise were then used in all subsequent tests on the patient. Radial pulse and ventricular apex rates were determined simultaneously for 30 seconds in each test, (a) just before the exercise was begun, (b) 30 seconds after the exercise was over and every minute thereafter for at least 9 minutes. Before each exercise period the patient was allowed to rest in the sitting position for 15 minutes or more until the basal control rates were stabilized as checked by three consecutive readings. Only one exercise test was performed at each clinic visit. The effect of digitalis was then determined by repeating the same exercise at various stages of digitalization. In most of these patients the effect of digitalis was studied by repeating the control and digitalization periods several times.

**Results.** The results can best be presented by giving typical curves in 4 of the patients representative of several similar curves obtained on these and the other 4 cases.

**Clinical Notes.** Case 1.—R. C., a white male, aged 35, had rheumatic heart disease with mitral stenosis and insufficiency and aortic insufficiency.

His first attack had occurred 13 years previously, and he had been known to have auricular fibrillation for at least 4 years. At the time of examination the patient had had no digitalis for at least 6 weeks. He complained of some shortness of breath on slight exertion, attacks of palpitation and a feeling of general weakness, but there were no signs of cardiac failure on physical examination. His basal exercise consisted of 12 trips on the Master stairs in 68 seconds. The acceleration in ventricular rate following the exercise and the augmentation of the pulse deficit are clearly shown (Fig. 1, Records A). After the patient had received digitalis gr. iii daily for 1 week and gr. iss daily for 2 weeks, he showed not only a slower basal ventricular rate and practically absent basal pulse deficit but also a smaller ventricular acceleration and practically no pulse deficit (Fig. 1, Records B). No clinical or

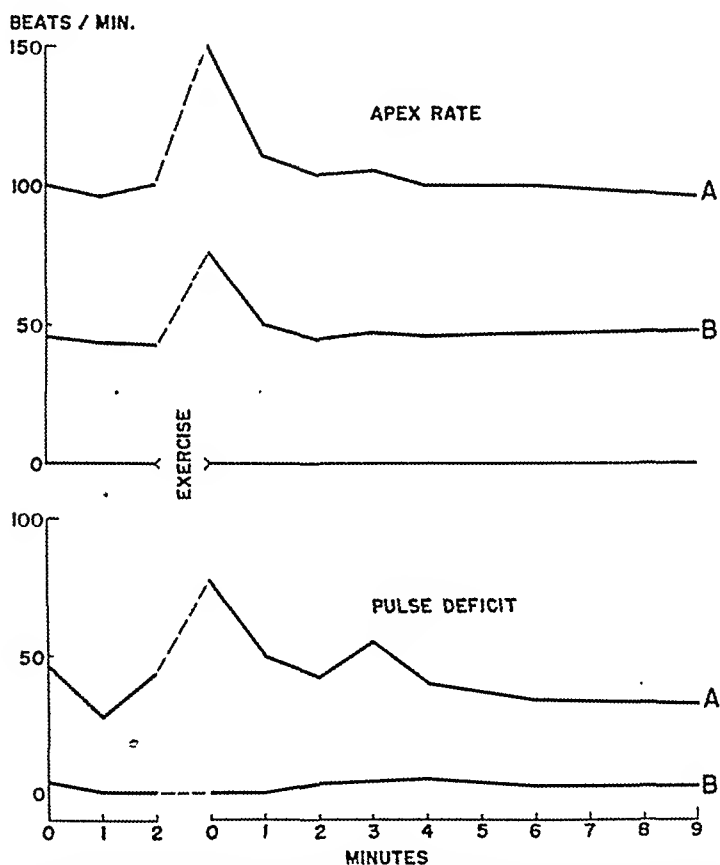


FIG. 1.—Effect of a standardized exercise on Patient R. C. Upper curves average apical ventricular rates; lower curves, pulse deficits. Exercise period is indicated by gaps in upper zero line. Discussed in text.

electrocardiographic evidences of digitalis intoxication were evident at this time and the patient stated that his shortness of breath, palpitation and weakness had disappeared. Digitalis had apparently not only slowed his basal rate but had lessened the effect of the standard exercise on his ventricular rate and the number of ineffective beats.

CASE 2.—A similar result was obtained on a second patient, A. S., a white male of 44 years, with rheumatic heart disease, mitral insufficiency and auricular fibrillation who had known that he had "heart trouble" for 7 years. At the time of examination the patient had stopped digitalis for

6 weeks. He complained of general weakness and shortness of breath even at rest. He appeared to be slightly cyanotic and had râles in both lung bases, a tender liver and slight ankle edema. His exercise at this time was 12 trips in 70 seconds (Fig. 2, Records A). Three weeks later after digitalization (20 gr. were given in the first 4 days followed by gr. iss daily), the signs and symptoms of cardiac failure had disappeared and there was no evidence of digitalis intoxication. The exercise test at this time gave results in all details exactly as in the preceding case (Fig. 2, Records B). The maintenance dose of digitalis was then reduced to gr. i every 2 days and 3 weeks later the exercise was repeated (Fig. 2, Records C). It will be seen that the

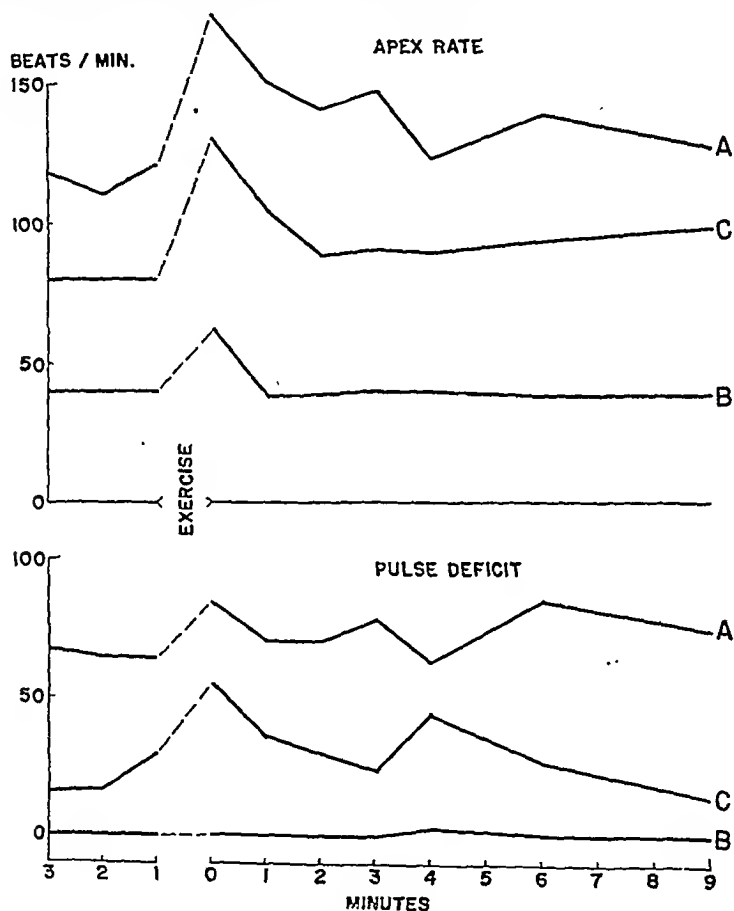


FIG. 2.—Effect of a standardized exercise on Patient A. S. Constructed as in Fig. 1. Discussed in text.

curves are intermediate between A and B and represent partial digitalization. Although the patient did not present any evidence of heart failure at this time, he stated of his own accord that he felt better while taking the larger doses of digitalis. Apparently, complete digitalization was necessary in this patient to minimize the effects of exercise on heart rate and the number of ineffective beats.

When the ventricular rate is around 60, under the basal conditions, digitalis has little or no effects on the action of exercise (Fig. 3). Curves A were taken when the patient J. K. had been off digitalis for 3 weeks.



CASE 3.—J. K., a white male of 58, had had evidence of mild heart failure for 5 years. His chief complaints were dyspnea after walking a block, orthopnea and occasional attacks of precordial pain. There was evidence of left ventricular enlargement and slight edema. Blood pressure was 140/85. The origin and auricular fibrillation were confirmed. Despite the presence of mild heart failure, the effect of exercise (8 trips in 65 seconds), is similar to that in the fully digitalized states of the other patients. The patient was put on digitalis gr. iii daily for 4 weeks and then the same exercise was repeated. The results are shown in Records B, which are similar to A except that the basal apex rate is at a slightly lower level. The patient at the time of the second test had noticed no change in his condition while on the digitalis and his physical findings were also unchanged at this time.

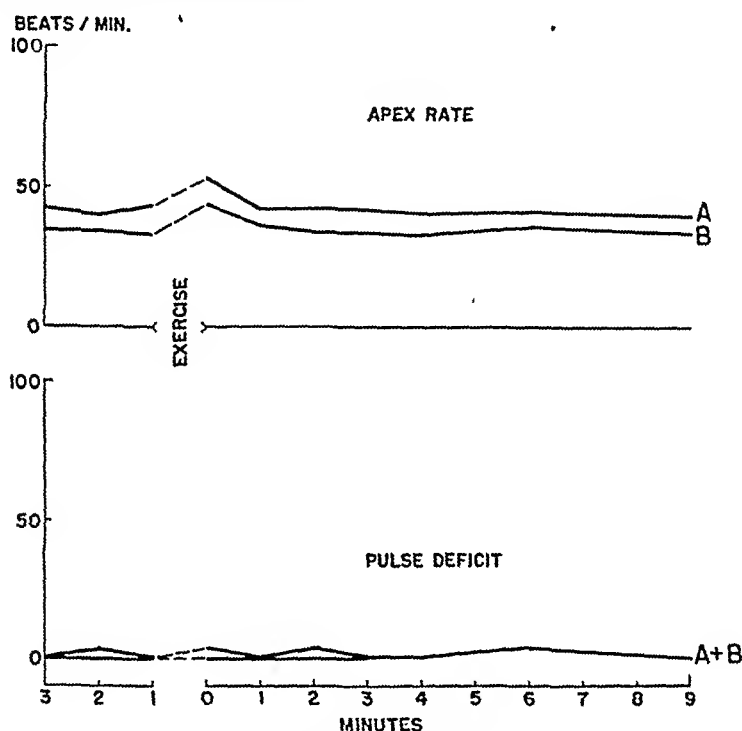


FIG. 3.—Effect of a standardized exercise on Patient J. K. Constructed as in Fig. 1. Discussed in text.

The lack of effect of digitalis on the exercise test was characteristic of all 4 cases of auricular fibrillation on a coronary sclerosis basis having a slow basal ventricular rate, and suggests that when the A-V conduction is noticeably impaired before medication, digitalis exerts little or no further action.

When digitalis was seemingly without effect in one patient, the usual digitalis action was readily obtained when this patient was placed in the hospital and given similar doses of digitalis (Fig. 4).

CASE 4.—A. F., a white woman of 51, had rheumatic heart disease and mitral stenosis occurring with her first attack of rheumatic fever 34 years before. She had had her first attacks of paroxysmal auricular fibrillation 2 years previously. When this patient had been without digitalis for some time,

the exercise which consisted of 11 trips in 90 seconds, produced a moderate acceleration and no added pulse deficit (Fig. 4, Records A). At the time of the test the patient's sole complaint was a feeling of weakness, but there were no signs of failure on physical examination. After the control exercise test, the patient was put on digitalis gr. iii b.i.d. for 1 week, gr. iii daily for a second week and then gr. iss daily for a third week, at which time the exercise test was repeated. The curves obtained were similar to the control except that the apex rate was at a slightly lower level. Following this, digitalis

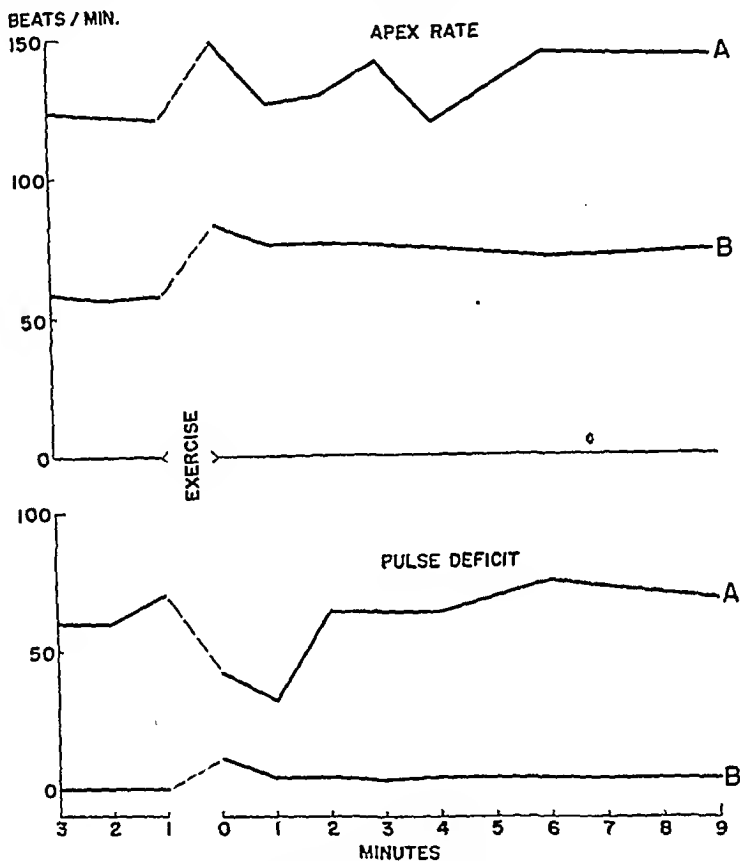


FIG. 4.—Effect of a standardized exercise on Patient A. F. Constructed as in Fig. 1. Discussed in text.

dosage was increased to gr. iii daily and at the end of 3 weeks an exercise test again gave results similar to the control. After 3 more weeks at a dosage of gr. ivss daily the exercise test again gave results differing little from those of Records A. It was therefore decided to place the patient on absolute bed rest in the hospital. This procedure without change in the dose of digitalis, rapidly led to a slowing in ventricular rate, so that within a week the dose of digitalis could be gradually reduced from gr. ivss to gr. iss daily. The exercise test was taken at the end of the week, but the duration of exercise was 5 instead of 1½ minutes (Fig. 4, Curves B). It will be seen that despite the greater amount of exercise, the exercise produced less change in ventricular rate than before digitalis was administered. At this time she stated that she could have kept up the exercise indefinitely.

**Discussion.** Our results suggest that the lack of effect reported by Blumgart and Boas *et al.* in certain cases of auricular fibrillation

were due to incomplete digitalization on the one hand, or to the presence of a slow ventricular rate and small pulse deficit in the absence of digitalis. Inadequate dosage of digitalis and a slow ventricular rate in the absence of digitalis appear to be the two chief circumstances which prevent the effective action of digitalis during exercise and presumably during emotional upsets, but the last case we reported shows that in some instances protracted rest is also necessary before this digitalis effect can be induced.

It seems to us that this sedative effect of digitalis in the presence of physical and emotional exertion is an important factor contributing to the clinical improvement noted in such cases. The ambulatory cardiac patient is constantly subject to physical and emotional exertion as part of his everyday existence, and therefore is not under basal conditions most of the time. If these exertions are accompanied by a great acceleration of ventricular rate with an exaggeration of the pulse deficit in the absence of digitalis, then the work of the heart will be done less efficiently than when the rate is kept slow. Each contraction of the heart requires the expenditure of energy whether the beat is effective or not. In rapid irregular heart action the energy cost of the work is out of proportion to the amount of blood flow maintained.<sup>7</sup> When the heart is in a poor state or in incipient failure, rapid irregular heart action will lead, by itself, to an aggravation of the failure. Anything which can prevent this wastefulness during stress by preventing excessive acceleration of the rate and exaggeration of the pulse deficit will therefore lead to improvement of the patient's condition. This is one of the things digitalis can do.

Our experience, therefore, suggests that digitalis in maintenance doses not only reduces the basal ventricular rate and pulse deficit at basal conditions, but also can prevent the excessive acceleration of the ventricular rate and the exaggerated pulse deficit during physical and emotional exertion. In both ways digitalis protects the heart and permits it to meet the daily strains which ambulatory patients are subject to with less ill effect. While tachycardia is a means by which the heart can maintain an adequate circulation when its stroke output is reduced (Luten<sup>10</sup>, Wiggers<sup>14</sup>), it is not an efficient way. Tachycardia itself can lead to heart failure when it is excessive or when the heart action is very irregular (*cf.* Gross<sup>7</sup>).

The effectiveness of a given dose of digitalis will depend to some extent upon the natural balance of the action of the vagi and sympathetic nerves, and upon the adrenalin content of the blood, since these influence A-V conduction definitely (Carlen and Katz<sup>4</sup>), and these factors alter to a varying extent in different subjects.

Digitalis depresses A-V conduction (*cf.* Lewis,<sup>9</sup> Cushny,<sup>5</sup> and Weese<sup>13</sup>), in part by a direct action and in part through stimulation of the vagi. Gold *et al.*<sup>6</sup> have shown that the vagus action predominates with smaller doses and the direct action with larger doses of

digitalis. Obviously when the A-V conduction is naturally depressed as in the slow ventricular rates of auricular fibrillation on a coronary sclerosis basis, digitalis can do little more in this regard. In these cases Nature has done what digitalis does in patients with auricular fibrillation and rapid ventricular rates (Mackenzie,<sup>11</sup> and Robinson<sup>12</sup>).

This study suggests a method by which the adequacy of digitalis medication in a patient with auricular fibrillation may be tested. It would appear that the aim should be to give that amount of digitalis which not only keeps the basal rate slow but minimizes the acceleration of the ventricular rate on standardized exertion.

**Summary.** Digitalis, when used in large therapeutic doses was found to lessen the ventricular acceleration which occurs following a standardized exercise test in ambulatory patients with auricular fibrillation. It also decreased the pulse deficit at the same time. It was not effective in patients who already had a slow ventricular rate. Protracted rest, as well as large doses, may be required to produce slowing.

The tendency to prevent acceleration during exertion and emotional stress represents one of the modes of clinical benefit derived from digitalization.

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### CIRCULATION TIME (MAGNESIUM SULPHATE METHOD) IN THE DIAGNOSIS OF PERIPHERAL VASCULAR DISEASE.\*†

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LITTLE consideration has been given in the past to the circulation time within any part of the vascular circuit which included within it, to a large extent, the arterial supply of the extremities.<sup>4,28,29,35,43,45,47</sup> Yet, it would seem plausible to suppose that

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individuals with vascular disease of the limbs might display circulation times to the tips of the extremities different from that of normals. Should this actually be true then the determination of the circulation time to the tips of the extremities would find application as a diagnostic test of the presence or absence of peripheral vascular disease. In order to evaluate that supposition, this study was undertaken to determine what might be the normal circulation time from the arms to the tips of the extremities and to compare these times with similar times obtained in known cases of peripheral vascular disease.

*Selection of Patients.* Two hundred "normal" individuals were selected from the ward and clinics of the hospital and from volunteers, all of whom were free of clinical peripheral vascular disease. Excluded were cases with cardiovascular disease, pulmonary disease, fever, anemia or other diseases of the blood or metabolism. Upon these were performed 405 complete tests, or, counting each extremity, 1593 tests.

Twenty-one cases of peripheral vascular disease were chosen from among the attendants at the Vascular Clinic and hospital patients admitted because of peripheral vascular disease. All of these patients were free at all times of cardiac decompensation. Upon these were performed 83 complete tests or, counting each extremity, 332 tests.

*Agent Used.* Blumgart and Yens<sup>8</sup> have postulated the essential requirements that any substance must fulfill in order to be suitable for use in the determination of circulation time. Magnesium sulphate, originally suggested by Zwillinger,<sup>51</sup> has been successfully used by several investigators in determining circulation time.<sup>6,42,47</sup> In this study magnesium sulphate was selected as the agent after analyzing it in the light of the postulates of Blumgart and Yens.

The substance when given intravenously was non-toxic and harmless. The end reaction was sharp and sudden. In a group of 43 normal individuals the net effect of the magnesium sulphate was negligibly to reduce both phases of the blood pressure (1.5 to 4.0 mm. of Hg) and negligibly to reduce the pulse rate (1 per minute). Rapid repetition of the test on each of approximately 100 individuals permitted the conclusion that magnesium sulphate could be reinjected into the same individual at intervals as short as 5 minutes without materially altering the accuracy of the circulation times obtained. No thromboses and no sloughs were encountered in over 500 injections although paravenous infiltration did produce pain and tenderness for a short period. The salt is easily obtained and its preparation for suitable intravenous injection is so simple that the cost is practically nil.

It was felt, therefore, that magnesium sulphate met all the requirements of a substance suitable for use in the determination of circulation time with the sole exception of the requirement demanding no coöperation on the part of the patient.

*Method. Solution.* Ten per cent C.P. magnesium sulphate solution in distilled water stored in ampoule vials and autoclaved.

*Dosage.* 5 cc. of the 10% magnesium sulphate given intravenously.

*Rate of Injection.* Every effort is made to secure as rapid an introduction of the solution into the vein as possible. By experimentation with various sized syringes and needles it was found that the most rapid injection time followed the use of a 10 cc. syringe and a No. 18 gauge needle (0.4 to 0.8 sec.).

*Technique.* All patients were tested under as basal a condition as the clinical circumstances permitted. The individual, at least 3½ to 4 hours

having elapsed since the last meal, was placed at bed rest in the dorsal decubitus for a period not less than 10 to 15 minutes. Most patients were already at bed rest when approached for the performance of the test. Those who were ambulatory, and in particular those who were in attendance at the various out-patient clinics, were first permitted to sit about quietly for some time before the additional bed rest, just preceding the injection. A detailed explanation was made to every patient as to the nature of the procedure about to be performed, the sensations to be expected, the manner in which the end points were to be announced and the general import of the test. By these means an attempt was made to allay anxiety and nervousness, obviate apprehension and secure the intelligent coöperation of the individual. The arm was supported upon a pillow on a level approximately with the entrance of the venæ cavæ into the right auricle. Either arm was used and in many individuals repeated tests were made in alternate arms. Following the proper preparation of the antecubital space, the needle was engaged into the most accessible antecubital vein and the tourniquet was then removed. A few moments were permitted to elapse so as to allow the patient to regain his composure. During this interval there was again described the warm sensation that would appear in the back of the tongue and sweep down the body to the tips of the extremities. On the "3" the watch was started simultaneously with a rapid injection of the material. At the first perception of warmth at the tongue and at the tips of each extremity the patient cried out loudly "tongue," "right hand," "left hand," "left foot," "right foot," "both hands," or "both feet," as the case might be. Two minutes were allowed for sensations to appear at all the end points. Any end point not registering a sensation in that period of time was labeled as a "blank." Should that same extremity yield no sensation on 2 or more repeated tests, the tests were held to be "persistent blanks."

**Results.** There is a clear prolongation of the average circulation time from the arm to the tips of the extremities in the peripheral vascular disease group as compared with the normals (Table 1). But, there is apparent a wide overlapping of the ranges of the normal and of the peripheral vascular disease groups (Table 1) which would tend to invalidate any conclusive comparisons of average times.

TABLE 1.—ARM-TO-HAND AND ARM-TO-FOOT CIRCULATION TIMES.

	No. of individuals		No. of tests.		Range.		Average time (sec.).		Average deviation.	
	N.	PVD.	N.	PVD.	N.	PVD.	N.	PVD.	N.	PVD.
Arm-to-rt. hand	200	21	405	83	6.0-61.3	12.2-54.0	19.3	25.7	±5.2	±6.3
Arm-to-lt. hand	200	21	401	83	6.0-52.2	14.1-66.4	19.1	24.5	±4.9	±6.3
Arm-to-rt. foot	199	21	392	83	7.4-50.1	18.0-70.1 (117.2)	23.8	35.7	±6.0	±10.4
Arm-to-lt. foot	200	21	395	83	8.2-56.2	18.0-75.0	24.4	36.1	±6.7	±10.9

In the peripheral vascular disease group as compared with the normals, more than twice as many individuals and almost three times as many tests yielded "blanks" at some time or other, while more than three times as many individuals and almost twice as

many tests yielded "persistent blanks" (Table 2). This is more striking when one considers that over two-thirds of all individuals with peripheral vascular disease display "blank" reactions at some time or other.

TABLE 2.—DISTRIBUTION OF BLANK TESTS—ALL EXTREMITIES.

	No. of ind. tested.	No. of tests performed.	Blanks.				Persistent blanks.			
			Ind. rep.	Total ind., %.	No. tests.	Total tests, %.	Ind. rep.	Total ind., %.	No. tests.	Total tests, %.
Normals	200	1593	64	32.0	211	13.3	15	7.5	84	5.3
Entire group PVD.	21	332	14	66.7	112	33.8	5	23.8	33	9.9

It seems that a "blank" reaction might be in part a manifestation of a circulation time so prolonged that no terminal sensation was manifest. To support this hypothesis we were able to demonstrate longer average circulation times in those individuals who never experienced "blanks," as compared to those who did experience "blanks" at some time or other. Hence, were it possible to attribute a numerical value to each "blank," it would appear that the average time obtained in the peripheral vascular disease group would far exceed that of the normals and the average ranges would become so far separated from each other that there would be no longer the overlapping observed. Furthermore, it was noted throughout that the greater the number of tests performed on any one individual, the less the likelihood of obtaining "persistent blanks" except in those with peripheral vascular disease.

With the thought in mind that the longer circulation times in the peripheral vascular disease class may be in some way related to the older age groupings of the peripheral vascular disease patients, a comparison was made in the normal group (where the sample was sufficiently large) of the average circulation times in the various age classes. Both the arm-to-tongue and the arm-to-extremity times showed a definite trend toward the prolongation of circulation time with advancing age.

An attempt was made to classify the 21 patients with known peripheral vascular disease on the basis of the severity of their disease into "severe," "moderate," and "mild" groups. No single definitive measure was used to separate these, but rather a combined clinico-laboratory evaluation. A comparison of the average times in these groups revealed a definite and distinct prolongation of the circulation time parallel with the degree of peripheral vascular impairment.

In like manner, it appeared that the average circulation time from the arms to the tips of the extremities was longer to the more involved extremity than it was to the opposite one

**Comment.** A striking and important fact that was evident throughout this study was the great variation in circulation times obtained both in the same and between different individuals. It would seem that there are either inherent in the method or linked with the long circulatory pathway several influences that tend to induce varying results even in the same individual.

*First*, there is an inadequacy in the method. The use of magnesium sulphate renders the determination of the circulation time purely a subjective one. On that account, "circulation time" becomes really "circulation time" plus "reaction time" on the part of the patient as well as on the part of the observer.

*Second*, there are present before and during the performance of the test many physiologic factors which produce marked variations in the blood flow in the extremities. These include: 1, spontaneous variation in vasomotor tonus;<sup>1,13,15,17,19,21,24,36,37,38b</sup> 2, varying environmental conditions;<sup>1,13,15,17,19,21,24,36,37,38b</sup> 3, traumatic stimuli;<sup>1,13,18</sup> 4, ingestion of food;<sup>1,38a</sup> 5, sleep;<sup>1</sup> 6, exercise;<sup>16,38b</sup> 7, sensory stimuli;<sup>18,21,41</sup> 8, pregnancy;<sup>6,22</sup> 9, age. Blumgart<sup>7</sup> concluded that the velocity of blood flow through the lungs showed no constant relationship to the age of the patient. Candel<sup>12</sup> likewise concluded that there was no correlation between age and circulation time. However, children have been shown to exhibit slightly more rapid circulation times than adults<sup>3</sup> and the results of our own studies would infer that the velocity of blood flow tends to diminish with advancing age.

*Third*, it has been adequately established that the velocity of blood flow varies with several pathologic states which may, in mild form, exist unrecognized in the individual being tested, such as anemia,<sup>9</sup> fever<sup>30,32</sup> and hyper- and hypometabolic states.<sup>7,20,39</sup>

An attempt was made in our material to eliminate or minimize these various influences through the selection of the subjects and the method of performance of the test as previously described. Yet, our success in so doing must, of necessity, have been variable and non-predictable. Because of this, it is apparent that a single determination of the circulation time from the arms to the tips of the extremities yields little information as to the average basal velocity of blood flow in the extremities of that individual.

The great preponderance of "blank" reactions in cases of peripheral vascular disease should be emphasized. It is extremely important, because of this, to appreciate that in the recognition of the presence of peripheral vascular disease from a study of the velocity of blood flow, the frequency and persistency of "blank" reactions is as much a determining finding as the actual circulation times obtained.

The explanation of why there should be longer circulation times and more "blank" reactions in cases of peripheral vascular disease affords interesting speculation. There are present in individuals with peripheral vascular disease several physico-anatomical changes



that would tend to retard the velocity of blood flow: These include: 1, Premature reduction in the head of pressure through overcoming the increased resistance encountered prior to the arteriolar-capillary junction. 2, Increased resistance to blood flow accruing from a combination of: (a) rigidity of the vessels; (b) encroachment on the lumen; (c) irregularity of the intima; (d) irregularity of the vessels. 3, Increase in the viscosity of the blood.<sup>5,31,40,46,49</sup> 4, Increase in cross-sectional area resulting from: (a) The development of collateral channels;<sup>2,11,36,48,49,50a,b</sup> (b) dilatation of vessels in territory deprived of blood;<sup>18,36</sup> (c) less intermission of capillary flow;<sup>10,14,23,25,27,33,44</sup> (d) loss of physiologic variability of the blood-vessels.<sup>2,34</sup> 5, Disorderly blood flow.<sup>2,36,48,49,50a,b</sup> 6, Dispersion of the test substance. 7, Possible higher threshold of stimulation of sensory end organs in areas with poor blood supply. 8, Possible concomitant cardiac inefficiency.

Patients with disease of their peripheral blood-vessels might well have concomitant disease of their coronary vessels and hence myocardial changes impairing the cardiac adequacy as a pump. To determine to what extent cardiac efficiency might affect the arm-to-hand and arm-to-foot circulation times, it was decided to evaluate the shorter arm-to-tongue circulation time in the same group. The latter is accepted as representing roughly the total cardiac circulation time, and, while not by any means conclusive, affords an isolated measure of the functional status of the heart. Accordingly, 340 tests were performed on 166 normal individuals and 74 tests were performed on the 21 individuals with peripheral vascular disease. Table 3 demonstrates a definite increase in the arm-to-tongue circulation time in the peripheral vascular disease group over that in the normals. Here, as in the arm-to-extremity times there is also overlapping in the average ranges, so that absolute and wide separation of the times are not possible.

TABLE 3.—ARM-TO-TONGUE CIRCULATION TIMES.

	No. of individuals.	No. of tests.	Range.	Average time (sec.).	Average deviation.	Blanks.	
						No.	Total tests, %.
Normals . . . . .	166	340	4.0-20.2	10.4	±2.0	3	0.9
Peripheral vascular disease . . . . .	21	74	8.0-26.3	13.5	±2.2	1	1.4

**Conclusions.** 1. By this method there seems to be some prolongation in circulation time in a *group* of patients with peripheral vascular disease as compared to normal subjects, and in *groups* of older subjects as compared to younger subjects.

2. There also seems to be an increase in the number of "blank" reactions in the same group of patients with peripheral vascular disease as compared to normal subjects.

3. *But*, individual variations and overlap are so great that this method cannot be recommended for testing the peripheral circulatory efficiency of a *given* patient.

**Summary.** 1. The arm-to-tongue and arm-to-extremity circulation times were determined upon 200 normal subjects and 21 patients with peripheral vascular disease through the intravenous injection of 5 cc. of 10% magnesium sulphate solution.

2. Individuals with peripheral vascular disease exhibited a tendency toward a longer circulation time and a definite increase in the number of "blank" and "persistent blank" reactions.

3. Wide variations in circulation times were obtained both in the normal and in the abnormal groups even within the same individual. The possible reasons for this were discussed.

4. The possible explanations for the prolonged circulation times and the greater number of "blank" reactions in peripheral vascular disease were discussed.

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## THE CLINICAL SIGNIFICANCE OF BILATERAL EDEMA OF THE LOWER EXTREMITIES.

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THE occurrence of edema of the lower extremities is such a commonplace phenomenon in medical practice, and has been so thoroughly studied, that it would at first thought seem unnecessary to write of its clinical significance. However, too frequently there have been brought to our attention cases with edema attributed to heart failure which when properly evaluated is clearly due to other conditions. Many patients are given digitalis for supposed congestive failure when their edema actually is due to varicose veins, nutritional factors, phlebitis, or other non-cardiac cause. A survey of several of the textbooks on diagnosis shows that too little emphasis is placed on the significance of varicose veins, posture and other simple factors in the production of edema. It was evident that a careful clinical study of a group of cases would be of value to determine the relative incidence of the causative factors in dependent edema.

With this in mind, we have recently collected from the Out-Patient Department of the Massachusetts General Hospital 100 unselected cases of bilateral edema of the lower extremities. Cases of uni-

lateral edema were not collected because they would obviously not be confused with edema due to congestive heart failure. Out-patients, coming because of varied complaints, mostly attended the general medical and surgical clinics. Such an out-patient series is thus comparable to the group of patients encountered in general medical practice. In addition, we collected 100 cases of bilateral edema of the legs from the medical and surgical wards.

The essential criterion in the selection of cases has been that the patients must show to us definite palpable edema of the feet, ankles or pretibial areas. The hospital ward group was for the most part made up of bed patients at the time of examination, while the out-patient group was ambulatory and examined in the morning at the time of admission after they had been up and about for several hours. They were not selected on the basis of history, routine physical examinations and laboratory studies; in some instances, special laboratory procedures were also done. The edema was classified as slight, moderate, or marked, *i. e.*, minimal pitting of ankles or pretibial regions (slight), more pronounced edema reaching to the mid-leg (moderate), or severe swelling up to and above the knees (marked). An attempt was made to determine carefully in each instance the various factors involved in the causation of the edema.

**Analysis of Material.** *The Out-Patient Department Group.* (See Table 1.) It is quite evident that the largest number of cases is that due to varicose veins with or without obesity. Of the 56 cases in which varicose veins were important factors, the edema was slight in 34, moderate in 20 and marked in only 2 cases. On the basis of our experience and that of others,<sup>3,5</sup> uncomplicated varicose veins very seldom, if ever, cause marked edema (of the 21 cases, 16 were of slight and 5 of moderate amount). Varicose veins complicated by incompetent communicating veins, thrombophlebitis of the femoral or iliac veins, poor nutrition, congestive failure, obesity, and so on, may be associated with more severe degrees of edema.

It will be noted that there were only 13 cases due to congestive heart failure, and an equal number due to obesity alone. Of the 3 cases attributed to nutritional deficiency states, 1 had a gastrointestinal malignancy, and the other 2 were the result of dietary deficiencies. Lymphedema (due to chronic epidermophyton infection and to recurrent inflammatory processes of unknown origin) nephrosis, acute nephritis and cirrhosis of the liver were infrequent contributors to this group.

Of the remaining 6 cases in the miscellaneous group, 1 of rheumatoid arthritis had slight edema of obscure origin; in a cancer of the cervix with metastases to the liver, the edema most probably was due to circulatory obstruction; 1 had bilateral phlebitis of the femoral veins; 1 had myxedema; and there were 2 with no definite cause to be blamed for the edema. One of the last 2 cases had heart disease, but there was no evidence of heart failure, and digitalis

and other cardiac therapy were unsuccessful in relief of the edema; the other had edema for 10 or 12 years, during which time many studies were made but no cause for the edema found.

With regard to the symptoms in this group of cases, it was found that 71 complained of some degree of dyspnea (though only 22 had heart disease and only 13 of those had congestive failure). Among the 56 patients with varicose veins, 49 had dyspnea. This dyspnea

TABLE 1.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.  
(Distribution of Cases Seen in the Massachusetts General Hospital Out-patient Department.)

		Varicose veins—obesity.					Renal.							
		Varicose veins without obesity.			Obesity and varicose veins.		Heart failure.	Acute nephritis.	Nephrosis.	Nutritional.	Lymphedema.	Cirrhosis of liver.	Miscellaneous.	Total.
		Simple.	With phlebitis.	Obesity without var. v's.	Simple.	With phlebitis.								
Total cases		21	4	13	27	4	13	1	2	3	4	2	6*	100
Degree of edema	Slight	16	..	11	18	..	3	..	1	2	..	..	2	52
	Moderate	5	3	2	8	4	6	1	1	1	3	..	3	37
	Marked	..	1	..	1	..	4	..	..	..	1	2	1	11
Age	Under 40	2	..	4	1	1	1	1	1	..	2	..	3	16
	40 to 60	18	2	8	19	3	3	..	1	2	1	2	2	61
	Over 60	1	2	1	7	..	9	..	..	1	1	..	1	23
Sex	Male	6	1	..	6	..	8	1	2	1	2	2	1	29
	Female	15	3	13	27	4	5	..	..	2	2	..	5	71
Heart disease		..	..	..	7	1	13	..	..	..	..	..	..	22
Hypertension		6	1	2	8	3	10	1	..	1	..	..	..	32

\* One case of rheumatoid arthritis, 1 of carcinoma of the cervix with metastases to liver (marked edema), 1 of bilateral phlebitis of the femoral veins, 1 of myxedema 2 in which no definite cause could be given for the edema.

was on careful inquiry found to be clearly due to obesity, age of the patient, or poor physical condition, and was moderate in most instances. On the other hand, when patients presented the symptom of orthopnea, congestive failure was the cause of their edema in all cases except 1 (cirrhosis of the liver with ascites). We feel that whereas a complaint of dyspnea, palpitation and precordial pain may be elicited in many of these individuals with varicose veins and at first suggests a cardiac etiology, a careful evaluation of these symptoms and a thorough physical examination often are

necessary to determine whether the edema is due to heart failure or not. A little time spent in a careful investigation of these cases will more than repay itself by more accurate diagnosis.

*The Hospital Ward Group.* (See Table 2.) The predominant cause for edema was congestive heart failure (60 cases). The reason for the difference between this group and that of the Out-Patient Department is that the majority of the sicker patients were admitted directly to the hospital. It will be seen that many of the

TABLE 2.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.  
(Distribution of cases seen in Massachusetts General Hospital Wards.)

		Heart failure					Varicose veins.		Obesity.		Renal.													
		Total.	Uncomplicated.	With varicose veins.	With obesity.	With nutritional deficiency states.	Without obesity.		Without varicose veins.	With varicose veins.	Acute nephritis.	Nephrosis.								Nutritional.	Cirrhosis of liver.	Leukemias.	Myxedema.	Miscellaneous.
							Simple.	With phlebitis.																
Total cases		60	34	9	11	6	4	2	2	4	5	2	7	7	2	2	3*	100						
Degree of edema	Slight	8	6	1	..	1	4	1	2	2	1	..	6	..	..	..	1	25						
	Moderate	25	16	5	4	..	..	1	..	2	3	1	1	1	2	2	2	40						
	Marked	27	12	3	7	5	..	..	..	..	1	1	..	6	..	..	..	35						
Age	Under 40	14	7	1	6	..	..	..	..	..	4	2	2	1	..	1	1	25						
	40 to 60	27	19	3	3	2	2	..	..	2	1	..	2	6	2	1	2	45						
	Over 60	19	8	5	2	4	2	2	2	2	..	..	3	..	..	..	..	30						
Sex	Male	38	28	3	3	4	4	1	1	3	2	2	5	5	1	1	1	64						
	Female	22	6	6	8	2	..	1	1	1	3	..	2	2	1	1	2	36						
Heart disease	Total	60	34	9	11	6	1	..	1	1	1	..	..	1	..	..	..	65						
	Hypertensive	18	4	4	5	5	1	..	..	1	..	..	..	..	..	..	..	22						
	Coronary	19	13	3	2	1	..	..	..	..	..	..	..	1	..	..	..	20						
	Rheumatic	17	12	2	3	..	..	..	..	..	..	..	..	..	..	..	..	17						
	Ch. cor pulmonale	4	3	..	1	..	..	..	..	..	..	..	..	..	..	..	..	4						
	Luetic	2	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2						

\* One case of bilateral phlebitis of the femoral veins, 1 of rheumatoid arthritis, 1 of syringomyelia.

congestive failure cases were complicated. In the 6 cases in which heart failure was stated to be complicated by nutritional deficiency states, we have listed only those patients with evidence of severe deficiencies with low serum protein, and so on. Undoubtedly this is too low a figure, because many cases with congestive failure over a long period of time will have poor appetites and a dietary intake low in protein and lacking in vitamins. This quite likely is one reason why the usual treatment for congestive failure may in an occasional case not be completely effective.

The 7 cases caused by nutritional factors without heart failure included 3 instances of carcinoma of the stomach with poor dietary

intake, 1 of duodenitis and jejunitis with a very poor intake of food, bleeding gums, and a serum protein of 3 gm., 1 of regional ileitis with many operations, profound inanition and a serum protein of 4.4 gm., 1 of cancer of the lung, and 1 of chronic ulcerative colitis with a serum albumin of 2.9 gm. and globulin of 3.16 gm. per 100 cc.

Of the 2 cases of leukemia, 1 had chronic lymphatic leukemia with large glands in the inguinal region and some inanition which were probably the factors involved in the edema; the other had chronic myelogenous leukemia with infiltration of the liver and possibly some portal obstruction.

One case of syringomyelia of the cervical cord developed moderate edema. He was unable to use his lower extremities well and would sit in a chair for long periods of time. We were convinced that posture was the main cause of the edema in this instance.

The 30 remaining cases included 10 with varicose veins, 2 with obesity alone, 7 with cirrhosis of the liver, 5 with acute nephritis, 2 with nephrosis, 2 with myxedema, 1 with rheumatoid arthritis and 1 with bilateral femoral phlebitis.

A comparison of the out-patient and hospital groups is shown in Table 3.

TABLE 3.—BILATERAL EDEMA OF THE LOWER EXTREMITIES.

(Comparison of the Chief Clinical Causes in 100 Out-patient Department and 100 Ward Cases of the Massachusetts General Hospital.)

Cause.	O.P.D. cases.	Ward cases.
Varicose veins:		
Total . . . . .	56	10
Without obesity . . . . .	25	6
With obesity . . . . .	31	4
Heart failure:		
Total . . . . .	13	60
Uncomplicated . . . . .	13	34
Complicated . . . . .	..	26
Marked obesity alone . . . . .	13	2
Renal disease . . . . .	3	7
Nutritional . . . . .	3	7
Cirrhosis of liver . . . . .	2	7
Miscellaneous . . . . .	10	7
Total . . . . .	100	100

**Discussion.** Although this study has represented a fair cross-section of the various causes of edema, there are other factors to be considered. The effect of the upright posture in the production of edema needs emphasis. It is well known that the venous pressure in the ankles and feet in a standing normal individual may be very high (100 cm. or more).<sup>2</sup> Usually this is not important, because muscular movement in walking will promote both blood and lymph flow and thus compensate for such high hydrostatic pressures. However, if a normal person should stand in one position for an hour or more, slight edema of the ankles will occur.<sup>2,3</sup> Undoubtedly a number of old persons develop some edema of the lower extremities because they are inactive and sit for long periods. Many patients

who have been confined to bed for several weeks after an operation develop slight dependent edema during the first few days of convalescence. The presence of deep or superficial varicosities will increase, of course, the tendency to edema formation under such conditions. From a practical clinical standpoint, therefore, the factor of posture is an important one and should be considered in all cases of obscure edema.

The size of the patient's heart is a factor which must be given careful consideration. It is of considerable importance to realize that congestive heart failure does not occur without cardiac enlargement. Therefore, if we find the heart of normal size in the presence of edema of the legs we can rule out at once myocardial weakness and failure as the cause of such edema. The one interesting point about the possible relationship of a normal heart size with probable cardiac origin of the edema of the legs concerns the rare cases of chronic constrictive pericarditis in the series we are reporting herewith, but one should be on one's guard for such a case. If a patient with edema of the feet, or especially with enlargement of the liver and ascites, is encountered with normal heart size, engorged neck veins, and no obvious reason for the edema, one should think of the possibility of, and look for, constrictive pericarditis.

It is not within the scope of this paper to present in detail the pathologic physiology and mechanism of edema formation. This has been well discussed and summarized elsewhere.<sup>1,2,4,5</sup>

It becomes obvious, in view of our findings, that it is important to determine carefully the cause of edema in each individual case. Sometimes it will not be possible to do so, and after a careful study no clear-cut reason can be given for the edema, but in our experience such cases are exceptional. We would like to emphasize that when one is confronted with a case of edema, especially if it be slight or moderate, one should carefully determine the cause and not be too quick to attribute it to heart failure. Nor, on the other hand, should one say that the edema is due to some simple, relatively unimportant cause, unless an adequate study proves that to be true.

**Summary.** 1. Unselected cases of bilateral edema of the lower extremities (100 from the Out-Patient Department and 100 from the wards of this hospital) have been analyzed and the predominant causes of the edema and their frequency have been determined. In the out-patient group, which is analogous to a group of patients seen in general medical practice, the causative factors occurred in the following order of frequency: varicose veins (56 cases), with obesity (31 cases), without obesity (25 cases); obesity alone (13 cases); cardiac failure (13 cases); lymphedema (4 cases); renal disease (3 cases); nutritional factors (3 cases); cirrhosis of the liver (2 cases); and miscellaneous factors (6 cases).

2. The ward group showed the following frequency: congestive heart failure (60 cases); varicose veins or obesity alone or in com-



bination (12 cases); renal disease (7 cases); nutritional factors (7 cases); cirrhosis of the liver (7 cases); leukemia (2 cases); myxedema (2 cases); and miscellaneous factors (3 cases). The predominance of cases of heart failure in this group, in contrast to the former, is to be expected as only the sicker patients are admitted to the wards.

3. Thus it has been found that in an unselected group of ambulatory individuals with bilateral edema of the lower extremities, cardiac failure as an etiologic factor is less common than often thought. Varicose veins and obesity, with posture as a secondary or primary factor, are far more commonly responsible in such a group, particularly when the edema is slight or moderate in degree. Many such patients have symptoms which suggest a cardiac etiology, but careful study reveals that such symptoms are unrelated to organic heart disease and that the edema is the result of the less serious factors. We wish to emphasize that in a group of ambulatory patients, dependent edema infrequently indicates heart failure and therefore rarely requires digitalis therapy; such simple factors as varicose veins, obesity and posture, alone or in combination, are much more commonly the cause of the milder degrees of edema in such cases than is heart disease.

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### "PIGEON DERMATITIS," A VITAMIN B DEFICIENCY STATE WITH ANEMIA.\*

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THE classical experiments with beri-beri have been chiefly performed in pigeons.<sup>31</sup> When these animals are fed on a diet of polished rice, and at the same time given injections of thiamin chloride (vitamin B<sub>1</sub>), the development of beri-beri is prevented.<sup>32</sup> Upon continuance of this régime, characteristic symptoms develop in the course of 4 to 12 weeks. The animals lose considerable weight and

\* Aided by grants from the Commonwealth of Massachusetts, the Rockefeller Foundation, and W. P. A. Project 18088.

stand quietly for hours at a time with head on chest. The feathers become "fluffed out" and dirty in appearance, and the horny covering of the beak, legs and claws becomes dull and thickened. After 12 to 15 weeks, a well-marked anemia develops in association with hyperplasia of the marrow. The anemia and all the symptoms of this deficient state respond to therapy with liver extract and yeast, but no effect occurs when riboflavin, nicotinic acid, or the rat anti-dermatitis principle (vitamin B<sub>6</sub>) is administered. In many respects, the clinical picture of the deficiency corresponds closely to that of "chick pellagra" as described by Elvehjem *et al.*<sup>16</sup> The present communication deals chiefly with the clinical, hematological, and bone-marrow findings of this deficiency state and with the therapeutic effects of certain agents.\*

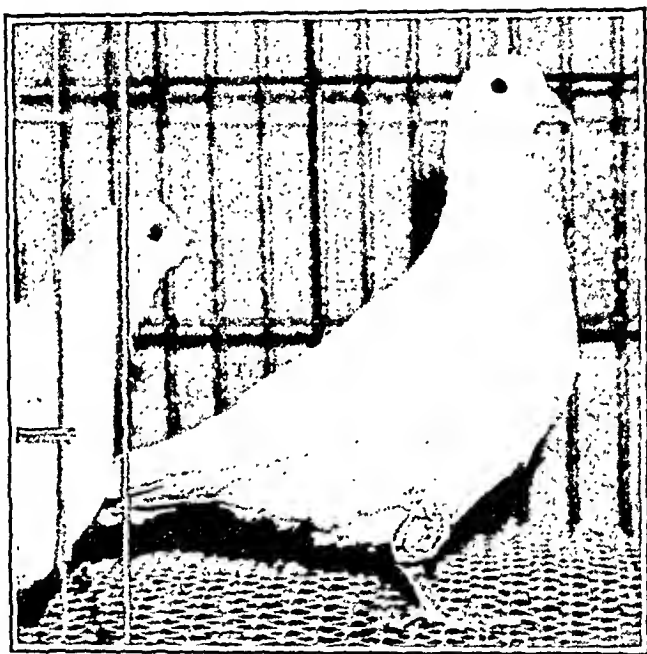


FIG. 1.—Normal pigeon. Note the "proud" erect position, and the sleek, smooth feathers.

**Methods and Materials.** White king pigeons, weighing from 300 to 550 gm. were used. After a preliminary period of observation of 2 weeks, during which time the animals were on a corn and grain diet, the diet was completely restricted to polished rice and water. This resulted in beri-beri within 2 to 4 weeks. To obtain a state of vitamin B<sub>2</sub> complex deficiency, vitamin B<sub>1</sub> was given by regular daily injections simultaneously with in-

\* We are indebted to Drs. Leo Alexander, Abraham Myerson, and Michel Pijoan for permission to utilize their pigeons (Series I, II, III, IV) for hematological studies. Dr. Alexander performed many of the postmortem examinations and Dr. Pijoan prepared riboflavin phosphate and "yellow ferment." Neurological studies in the deficient pigeons have been made by the above workers and a preliminary report was recently published (*Trans. Am. Neur. Soc.*, 64, 135, 1938). Other articles dealing with the neurological features of the deficiency state by the same authors are in preparation.

duction of the polished rice diet. The animals were weighed twice weekly and frequent observations were made of their physical status.

Blood studies were made weekly until the pigeons became anemic and at more frequent intervals when therapy with a specific substance was employed. The method of obtaining blood for examination in pigeons is

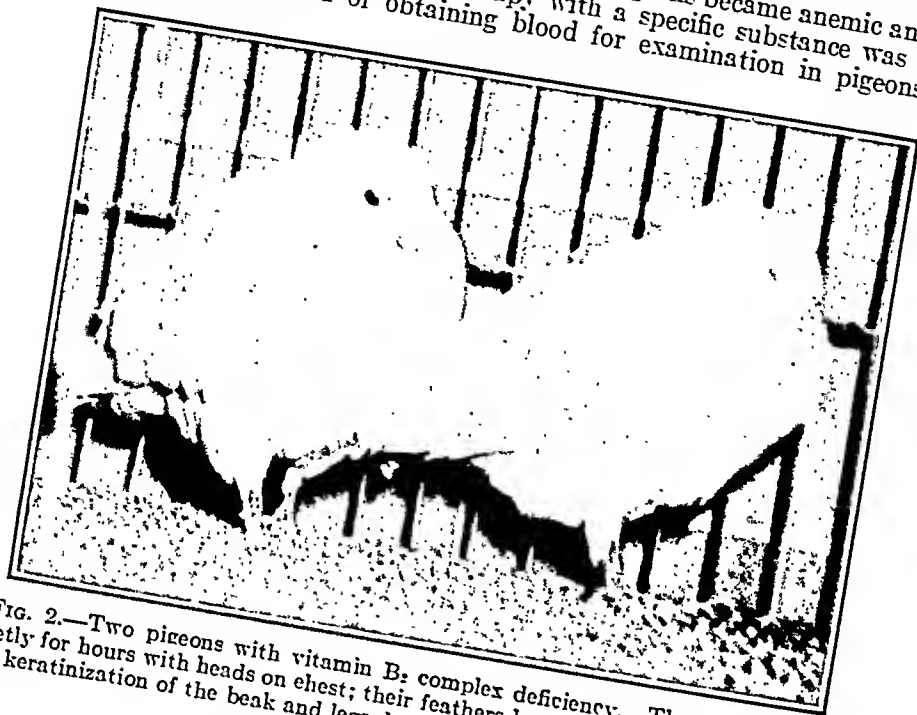


FIG. 2.—Two pigeons with vitamin B<sub>2</sub> complex deficiency. The pigeons stand quietly for hours with heads on chest; their feathers become dirty and "fluffed out," and keratinization of the beak and legs develop.

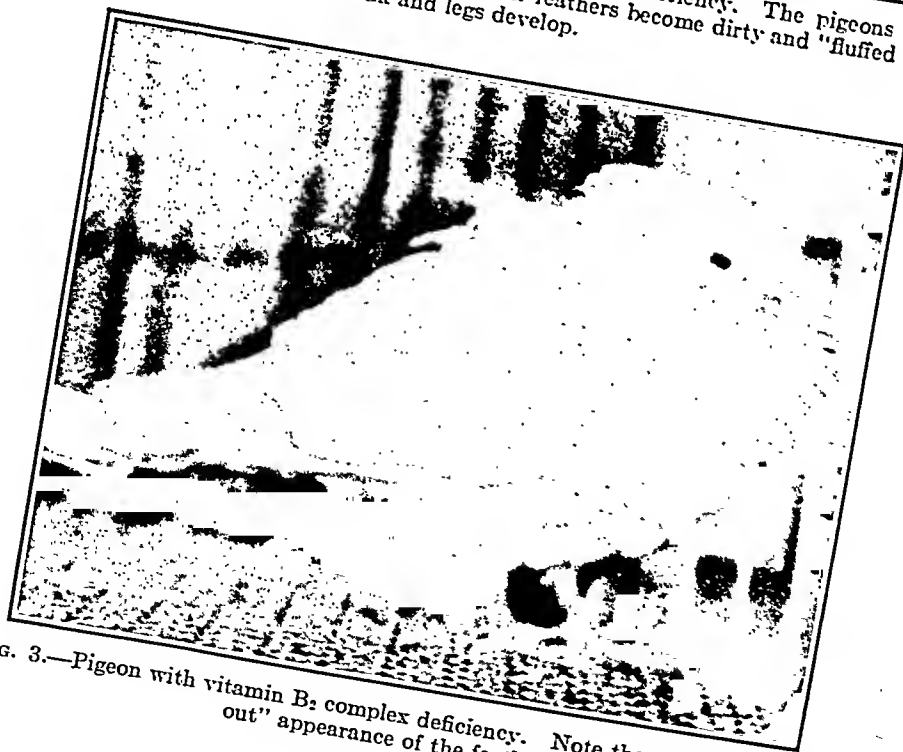


FIG. 3.—Pigeon with vitamin B<sub>2</sub> complex deficiency. Note the marked "fluffed out" appearance of the feathers.



FIG. 4.—Photomicrograph of a blood smear ( $\times 1520$ ) of a normal pigeon stained with brilliant cresyl blue and Wright's stain. Note that the nuclei of the reticulocytes are larger, rounder and less pyknotic than those of the non-reticulated erythrocyte.



FIG. 5.—Photomicrograph ( $\times 1520$ ) of stained blood smear of a pigeon with an induced B<sub>2</sub> complex deficiency state and severe anemia. Note the variation in size of the individual red cells. The nuclei show marked differences in size, shape, staining characteristics, and position.

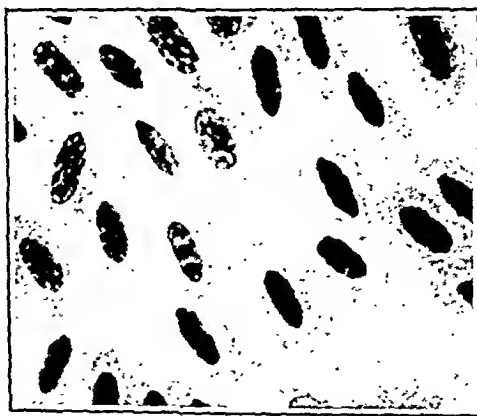


FIG. 6.—Photomicrograph ( $\times 1520$ ) of reticulocyte preparation from a vitamin B<sub>2</sub> deficient pigeon (Series VI, No. 17) 5 days after the administration of a dilute liver extract was begun. The reticulocyte count was 95% (!). Occasional reticulocytes are small, thick and heavily-stained.

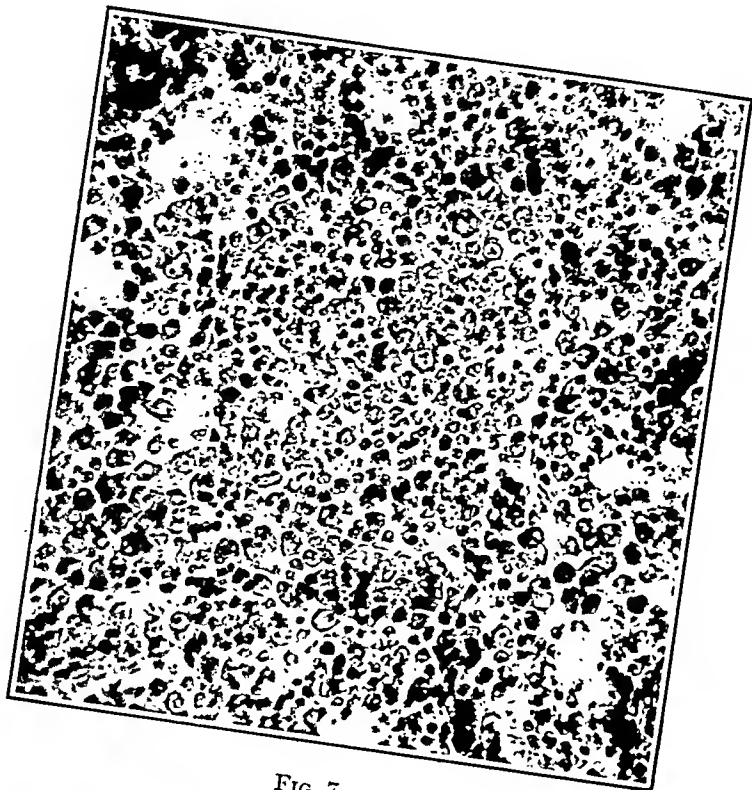


FIG. 7.

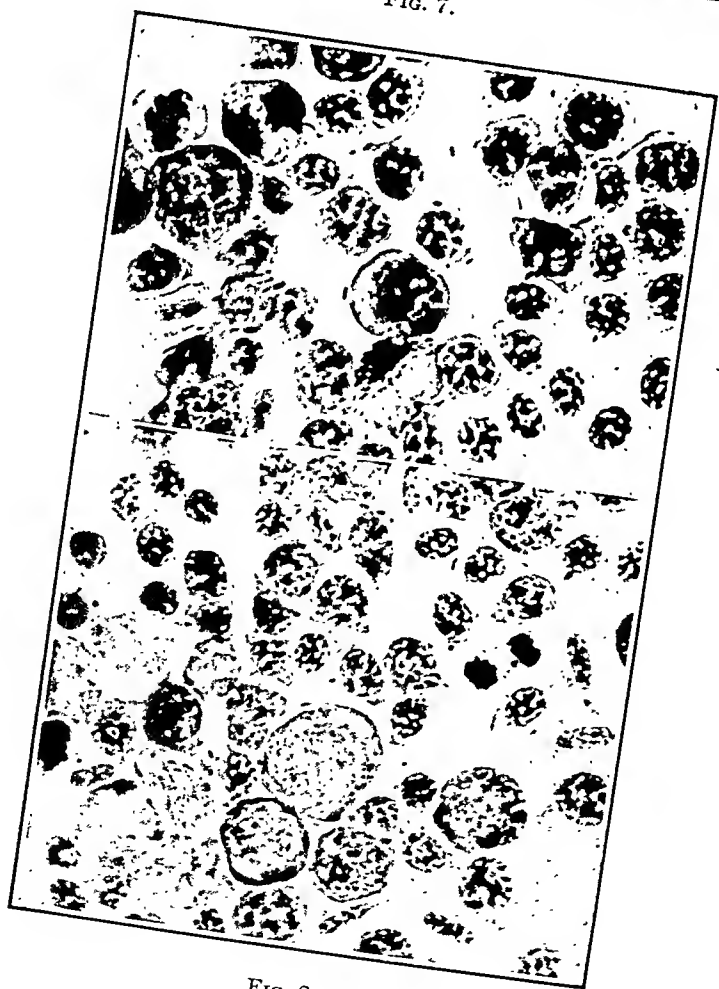


FIG. 8.

important and has not been sufficiently described in other publications dealing with the hematology of pigeons. Puncture of one of the large vessels under the wing was often attended with the loss of considerable blood, and at times exsanguination. The loss of blood attending such a procedure might well account for the considerable fluctuations in the reticulocyte counts of normal pigeons as noted by other investigators. On the other hand, use of one of the very small, just visible vessels nearby the large wing vessels, although occasionally successful, usually resulted in failure to obtain sufficient blood. An accidental puncture of the skin of the leg led to the discovery that good-sized, readily controlled drops of blood could be obtained from a small nick in the "red" skin of the leg.

Because of the well marked tendency of pigeon's blood to clot rapidly, two individuals are necessary in taking blood for counts. With the first drop, blood for hemoglobin is obtained, and immediately thereafter the red cell pipette is quickly filled by the second technician, following which smears are obtained. Pressure is then made over the puncture, which is covered with a bit of absorbent cotton.

Blood for hemoglobin, red blood cell count, and reticulocyte count was obtained. The hemoglobin was at first determined by the Sahli method (calibrated so that 100% = 15.5 gm.), and in the more recent and detailed experiments, by the Evelyn photoelectric method (100% = 15.6 gm.). The red cell counts were performed with United States Bureau of Standards pipettes and hemacytometers. Hayem's solution was found unsatisfactory because of its tendency to cause a murky solution with the pigeon's blood (hyperproteinemia?). On the other hand, a solution of sodium citrate 1.5% gave clear suspensions, and the tendency to clot formation within the pipette was prevented. Reticulocyte smears were made by preparing cover slips with a film of 1% alcoholic solution of brilliant cresyl blue, the usual 0.3% solution being found unsatisfactory, probably because of the greater absorption of dye by the nuclei of the red cells. Blood smears were made in the ordinary way and counterstained with Wright's stain—stain 1 minute, water 1 minute. If the second step in staining was longer than 1 minute, reticulocytes were frequently not visible, being now represented as polychromatophilic red cells. The staining of the reticulum substance was at times a variable phenomenon, and even with the utmost care, smears were occasionally obtained with polychromatophilic cells rather than reticulocytes. Furthermore, the reticulocytes at times exhibited variability in staining *even in the same smear*. In counting these cells it was absolutely essential to deal only with those sections of the smear in which the reticulocytes were well stained.\*

\* Nittis<sup>24</sup> has recently criticized the findings of previous workers with pigeons' reticulocytes. He rightly points out that in fresh preparations practically all the erythrocytes are reticulated. However, with the use of Dameshek's reticulocyte-platelet solution,<sup>6</sup> it is easily possible to distinguish the dense highly reticulated reticulocyte from those red cells which show only scattered granules. In "dry" preparations, the differentiation between reticulocytes and non-reticulocytes is readily made, not only by the reticulum present in the reticulocytes, but by distinct differences in morphology of the nuclear structure. These points will be covered in another communication.

#### LEGENDS FOR FIGS. 7 AND 8.

FIG. 7.—Photomicrograph (X 450) of femoral bone marrow section (Zenker's fixation; eosin-methylene blue stain) of a pigeon dying of vitamin B<sub>2</sub> deficiency. Note the marked cellularity of the marrow with the presence of large islands of primitive erythroblasts (erythrogonies). This marrow resembles that of human pernicious anemia.

FIG. 8.—Photomicrographs (X 1320) of stained bone marrow smear from pigeon dying of vitamin B<sub>2</sub> deficiency. The large primitive cells are erythrogonies and they are surrounded by early nucleated red cells (normoblasts A and B or pronormoblasts and erythroblasts).

Postmortem examinations were made of all pigeons which died. Particular attention was paid to the bone-marrow, although sections of the spleen, liver, and occasionally of other tissues were obtained. Bone-marrow (in "cylinders") was removed from the ulnas and femurs. Impression smears were immediately made from portions of these marrows and stained with Wright's stain (stain 6 minutes, stain and water 30 minutes). From these preparations, the morphology of the individual cells is readily studied and differential counts made according to the method of Dameshek and Valentine.<sup>7</sup> The following nucleated red cells are discriminated: Erythrogon (primitive nucleated red cell); Normoblast A (basophilic cytoplasm, but with definite red cell characteristics); Normoblast B (containing hemoglobin but not completely matured); Normoblast C (mature marrow erythrocyte). The entire cylinder of marrow was fixed in Zenker's solution, containing 5% of glacial acetic acid, and the sections stained with eosin-methylene blue.

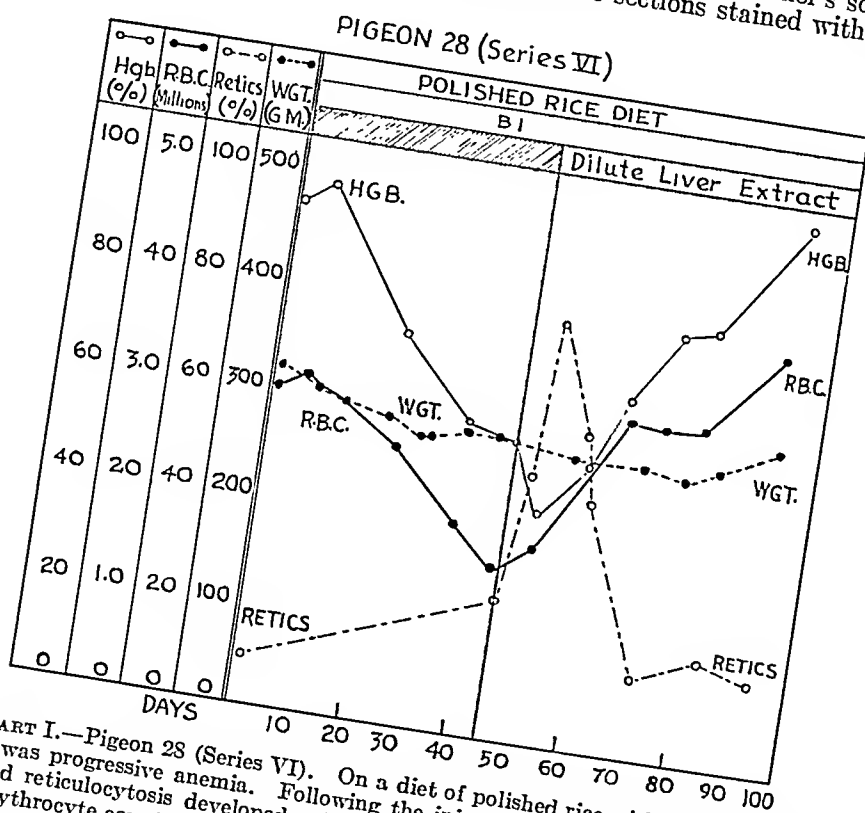


CHART I.—Pigeon 28 (Series VI). On a diet of polished rice with added thiamin there was progressive anemia. Following the injection of a dilute liver extract, a marked reticulocytosis developed, which was followed by increases in hemoglobin and erythrocyte counts above their original values.

The following materials were utilized during the course of the experiments:

1. Vitamin B<sub>1</sub> (thiamin chloride) (Winthrop Chemical Company, "Beritaxin"): 1 mg. tablets (containing 300 I.U.) were dissolved in 10 cc. distilled water. One cubic centimeter of this solution (containing 0.01 mg. of thiamin chloride) when injected intramuscularly every 2 days was more than adequate to prevent the development of beri-beri and was curative for beri-beri when this developed.
2. Riboflavin. (a) Riboflavin (Hoffmann-LaRoche, synthetic) given daily by intramuscular injection in dosage of 0.02 mg. (b) Riboflavin phos-

phate (phosphorolized for us by Dr. Michel Pijoan) in daily injections of 0.02 mg. intramuscularly. (c) "Yellow ferment"—daily intramuscular injections of 0.001 mg.

3. *Nicotinic acid* (Merck) given daily by intramuscular injection in dosage of 2 mg.

4. *Rat Anti-dermatitis Principle* (Vitamin B<sub>6</sub>). (a) *Crude*, obtained from yeast and prepared according to the method of Lepkovsky and Jukes,<sup>18c</sup> given daily by intramuscular injection in dosage of 0.5 cc. (b) *Factor 1* (Lepkovsky<sup>17</sup>)—crystalline. This pure material was kindly supplied by Dr. Lepkovsky and was given intramuscularly in daily dosage of 0.5 cc. (0.05 mg.).

# PIGEON 30 (Series VI)

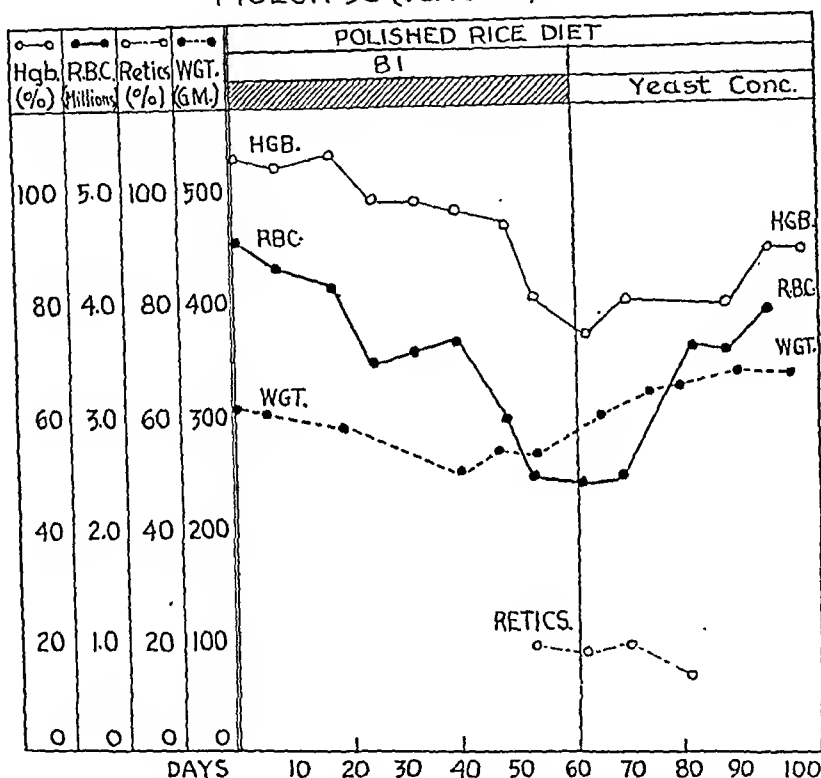


CHART II.—Pigeon 30 (Ser. VI). On a diet of polished rice with added thiamin, progressive anemia developed; this was readily controlled by the administration of yeast concentrate tablets orally.

5. (a) *Chick Anti-dermatitis Factor* (Elvehjem).<sup>35,20</sup> This purified (colorless) material was kindly supplied by Dr. Elvehjem and was given intramuscularly in dosage of 0.5 cc. every other day. (b) *Filtrate Factor(s)* or *Factor 2* (Lepkovsky). This material (a heavy brown liquid) was kindly supplied by Dr. Lepkovsky and was given orally in dosage of 0.5 cc. daily.

6. *Vitamin B Parenteral* (Lederle). According to the manufacturer each cc. contains besides B<sub>1</sub>, riboflavin 0.3 mg. (100 B-S units), nicotinic acid, dermatitis factor(s) 30 "rat day" units, and filtrate factors, approximately 30 "chicken day" units.

7. *Liver Extracts*: (a) Lilly "concentrated" liver extract for parenteral use. A relatively dilute extract of liver, 1 cc. being derived from 10 gm. of whole liver and containing 2 USP units per cc. Dosage 0.5 cc. by daily intramuscular injections. (b) Lilly "reticulogen" for parenteral use.



A highly purified and concentrated extract of liver, 1 cc. being derived from 100 gm. of whole liver. Dosage 0.5 cc. by intramuscular injection every 2 days.

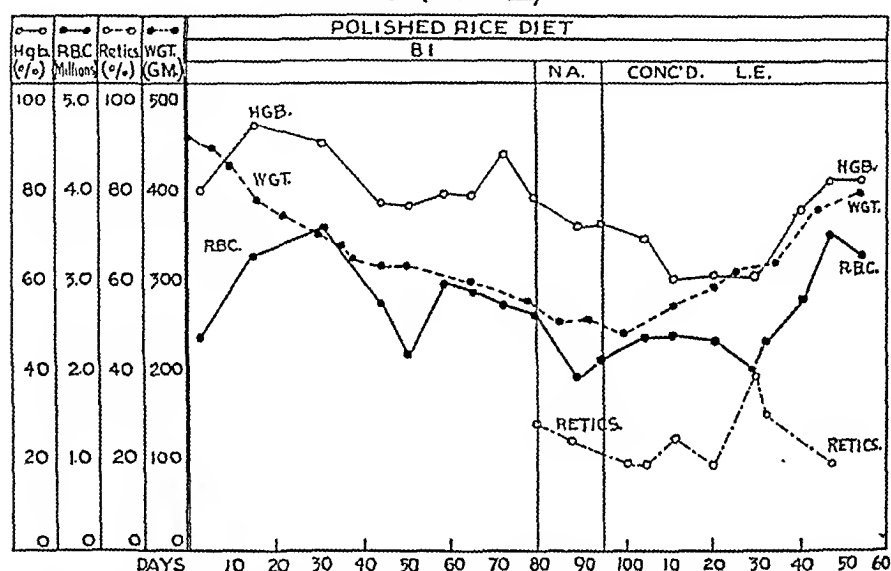
8. *Yeast Concentrate Tablets* (Mead's Brewers Yeast Tablets). 1 tablet (389 mg.) given orally, daily.

9. *Vitamin C*, ascorbic acid, synthetic (Hoffmann-LaRoche) 25 mg. given orally every 2 days.

10. *Iron citrate* injectable (Parke-Davis), 0.25 cc. given daily by intramuscular injection (containing 0.025 gm. of Fe citrate).

**Results. NORMAL PIGEONS AND NORMAL CONTROLS.** The normal pigeon is lively, moves about freely in his cage, and has smooth, clean feathers, which are "unruffled." The beak and the epidermis

PIGEON 23 (Series VI)



**CHART III.—Pigeon 23 (Ser. VI).** On a diet of polished rice with added thiamin, there were progressive reductions in hemoglobin, red cell count, and weight. Nicotinic acid given parenterally failed to stay the progress of the deficiency state, which was finally benefited by the persistent use of a highly purified and concentrated liver extract.

of the legs are smooth and of good color. The blood findings in our pigeons showed the following ranges: Hemoglobin (45 observations) 77 to 122%, average 92.8%; red cell count 2.24 to 4.57 (46 observations), average 3.22 millions; reticulocytes (40 observations) 10.8 to 14.6%, average 12.4%. Careful inspection of the nuclei of reticulocytes and non-reticulocytes disclosed that the nuclear structure in the non-reticulocyte (mature cell) is much more compact and pyknotic than in the relatively immature reticulocyte. In the latter cell, the nucleus is wider and larger and clear spaces in the nuclear structure are usually visible. The normal bone marrow is extracted from the femurs and the ulnas as firm, reddish cylinders.

The femoral marrow is normally red throughout its extract, but the ulnar marrow is usually fatty or flecked with reddish material. Differential counts of normal marrow impression smears (500 cells counted) give approximately the following findings:

	Per cent.		Per cent.
Femur: Erythroblastic cells:		Ulna: Erythroblastic cells:	
Erythrogonies . . . . .	2	Erythrogonies . . . . .	1
Normoblasts "A" . . . . .	10	Normoblasts "A" . . . . .	2
Normoblasts "B" . . . . .	10	Normoblasts "B" . . . . .	2
Normoblasts "C" . . . . .	25	Normoblasts "C" . . . . .	50
Mature erythrocytes . . . . .	20	Mature erythrocytes . . . . .	24
Leukocytes . . . . .	33	Leukocytes . . . . .	21

PIGEON 39 (Series VI)

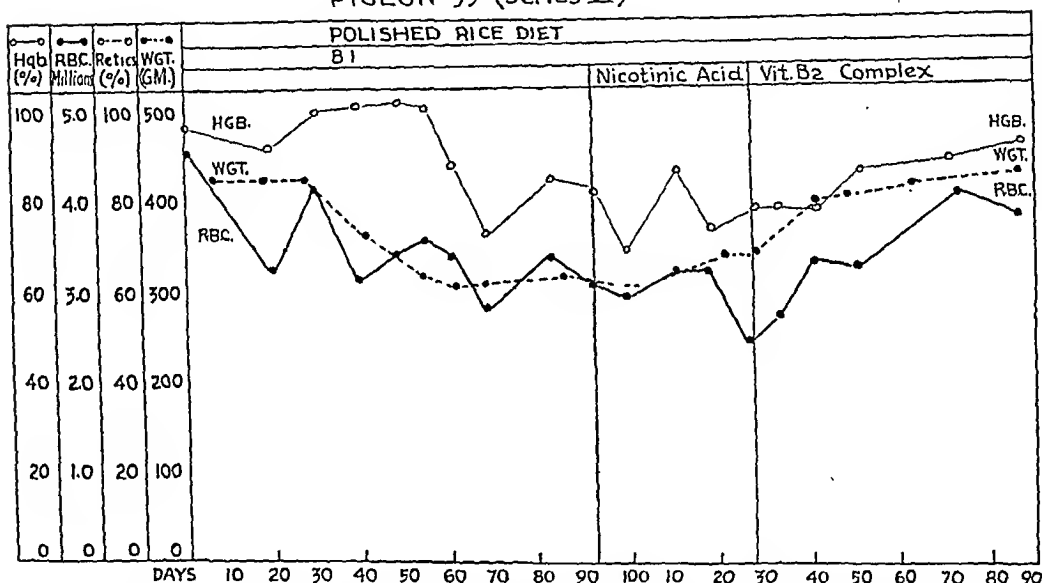


CHART IV.—Pigeon 39 (Ser. VI). Nicotinic acid was of no value in the treatment of the B<sub>2</sub> deficiency state, which was rectified by the administration of vitamin B complex given parenterally.

A detailed description of these cells is given in the paper of Dameshek and Valentine.<sup>7</sup> The smears from the femur were far more cellular and of better quality than those from the ulna; in many cases, the latter were too fatty to be properly stained or counted.

Sections of the normal marrows stained with eosin-methylene blue showed: *Femur*: A full, actively growing marrow with large groups of erythrocytes and leukocytic cells arranged in islands. The "blue" islands were for the most part early erythroblastic cells; these were usually in groups; the "red" islands, mostly granulocytes. Orderly maturation of cells from the most primitive to the most mature was clearly seen. Running throughout the section were always found branches of bone-marrow blood-vessels containing large numbers of closely packed mature erythrocytes. *Ulna*:

usually composed of one-half to two-thirds fat with small foci of both red and white cells. The vascular branches, containing mature, elongated, nucleated red cells, were quite prominent in these sections.

**STARVATION (Series II).** Complete starvation of the normal pigeon resulted in varying degrees of hypoplasia of the marrow. At the same time, the marrow of both the femur and ulna often took on a "disorganized" edematous appearance with the presence of fibrous tissue strands as a prominent feature. The degree of hypoplasia was subject to much individual variation. No blood studies were carried out in this series.

#### PIGEON 31 (Series VI)

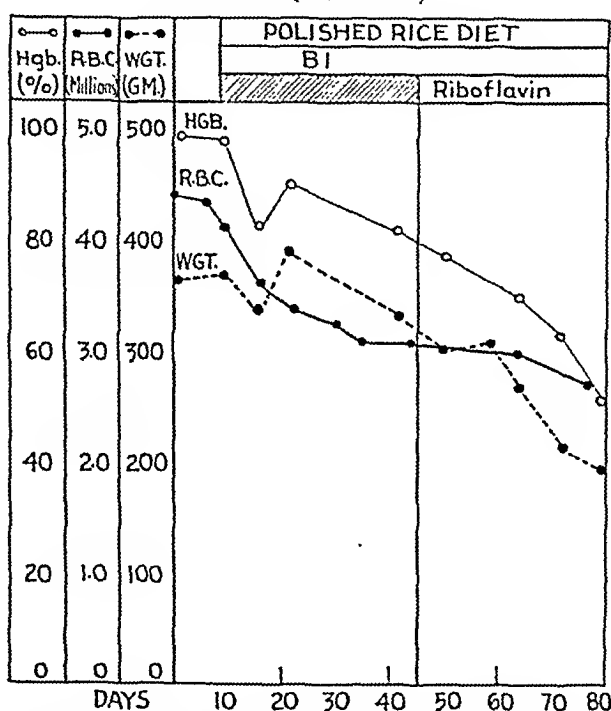


CHART V.—Pigeon 31 (Ser. VI). Riboflavin administered parenterally was of no value in the treatment of the  $B_2$  deficiency state induced by a diet of polished rice with added thiamin.

**COMPLETE  $B_1$  AND  $B_2$  DEFICIENCY (Beri-beri) (Series IV).** These animals died of classical beri-beri within 2 to 4 weeks. The condition of the marrow was variable, although marked changes were always present. In most cases, an edematous disorganized marrow was present with hypoplasia of the erythroblastic tissue. Usually, even with well-marked hypoplasia, islands of primitive cells interpreted as erythrogones were present. In some cases, these islands were quite prominent giving the appearance of hypercellularity; in these instances, the more mature forms of nucleated red cells were greatly diminished (*i. e.*, maturation arrest?). Large numbers

of small, round cells (lymphocytes? thrombocytes?) were often seen and at times the appearance of well marked lymphoid infiltration was presented. Evidences of increased blood destruction were usually present, *i. e.*, hemosiderosis, erythrophagocytosis of hemosiderin or broken down red cells by large cells (probably histiocytes). The leukocytic tissue, by contrast with the hypoplastic erythroblastic tissue, was usually very prominent and this apparent hyperplasia often resembled that due to infection.

### PIGEON 37 (Series VI)

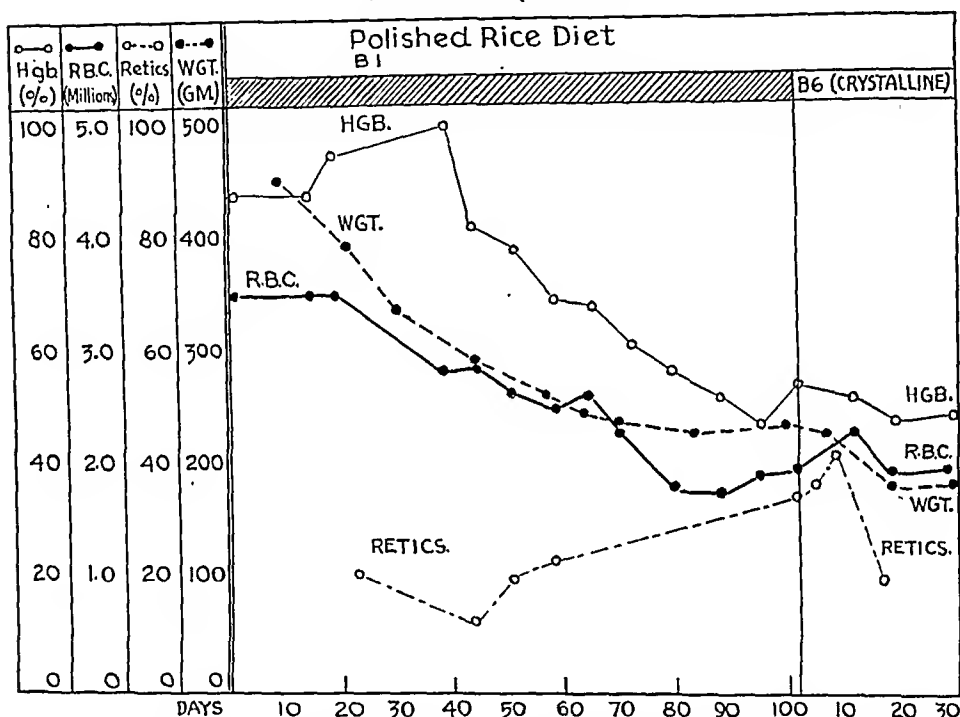


CHART VI.—Pigeon 37. The rat anti-dermatitis principle—vitamin B<sub>6</sub> crystalline—was of no definite effect in the amelioration of the B<sub>2</sub> deficiency state.

Blood studies of the pigeons with beri-beri were made in Series VI. Slight anemia developed, marked more by a reduction in hemoglobin than in the erythrocyte count. The average reduction in hemoglobin (10 birds) was 13.3% in an average time of 14.6 days. The erythrocyte count in the same birds dropped on the average only 0.17 million. In some birds, an actual increase in red cell count occurred. The accuracy of the counts in pigeons with beri-beri must be questioned in view of the marked changes in water balance which must inevitably take place. Furthermore, the apparent rise in red count of some of the pigeons may be due to dehydration, since with onset of beri-beri some of the birds became indifferent to their surroundings and did not take water.

To summarize, the bone marrow of the pigeons dying of beri-beri

generally showed evidences of hypoplasia with foci of primitive red cells (maturation arrest?) and at times hyperplasia of leukocytic tissue. Slight anemia usually developed, although the accuracy of blood counts in beri-beri is to be questioned in view of possible changes in water metabolism.

### PIGEON 44 (Series VI)

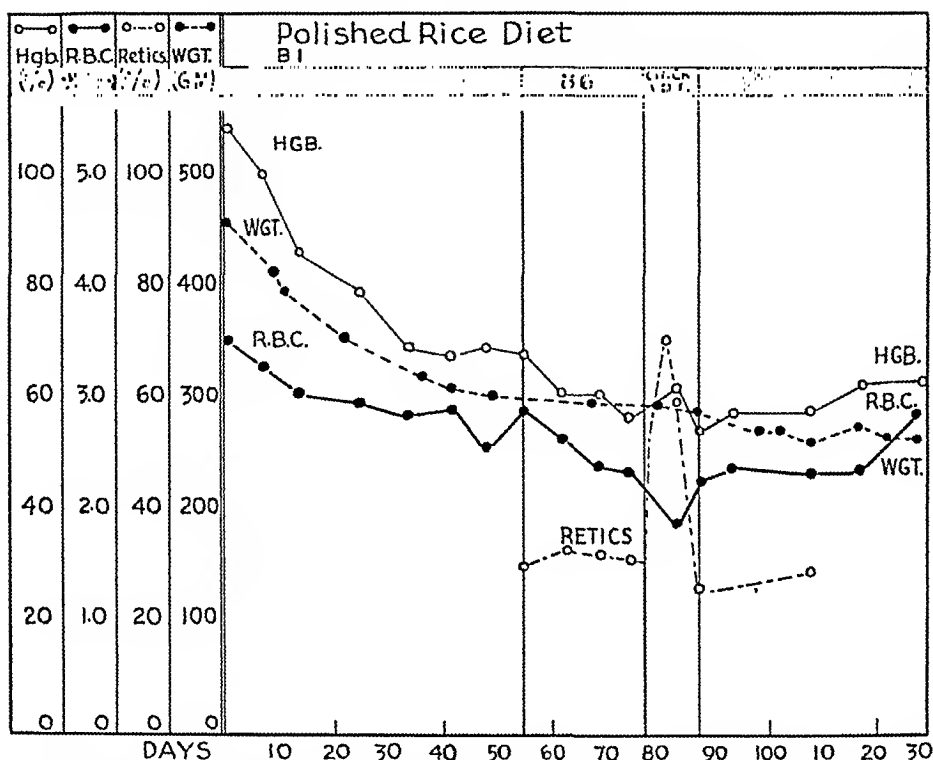


CHART VII.—Pigeon 44. Vitamin B<sub>6</sub> (crystalline) did not improve the B<sub>2</sub> complex deficiency state, nor did reticulocytosis develop. Upon administration of the chick anti-dermatitis principle, as purified by Elvehjem, a reticulocytosis ensued which was, however, not followed by an increase in the hemoglobin or red cell count nor by improvement in the pigeon's physical status.

**B<sub>1</sub> DEFICIENCY.** In 3 pigeons (Series IV, Group 4), a yeast extract free of B<sub>1</sub> was given simultaneously with the diet of polished rice, *i. e.*, beri-beri developed, although the B<sub>2</sub> complex was probably present in adequate amounts. In 1 of these animals, there was well marked red cell formation; in the other 2, hypoplasia of erythroblastic tissue was prominent. No blood studies were made in these animals.

**B<sub>2</sub> COMPLEX DEFICIENCY.** Pigeons fed on a diet of polished rice and water and simultaneously given daily injections of thiamin chloride (Vitamin B<sub>1</sub>) intramuscularly, lost weight fairly rapidly. The symptoms of beri-beri did not develop. For 2 to 4 weeks, the animals presented a fairly normal appearance, but between the 4th to 12th week, definite clinical changes became noticeable in most of the

## PIGEON 17 (Series VI)

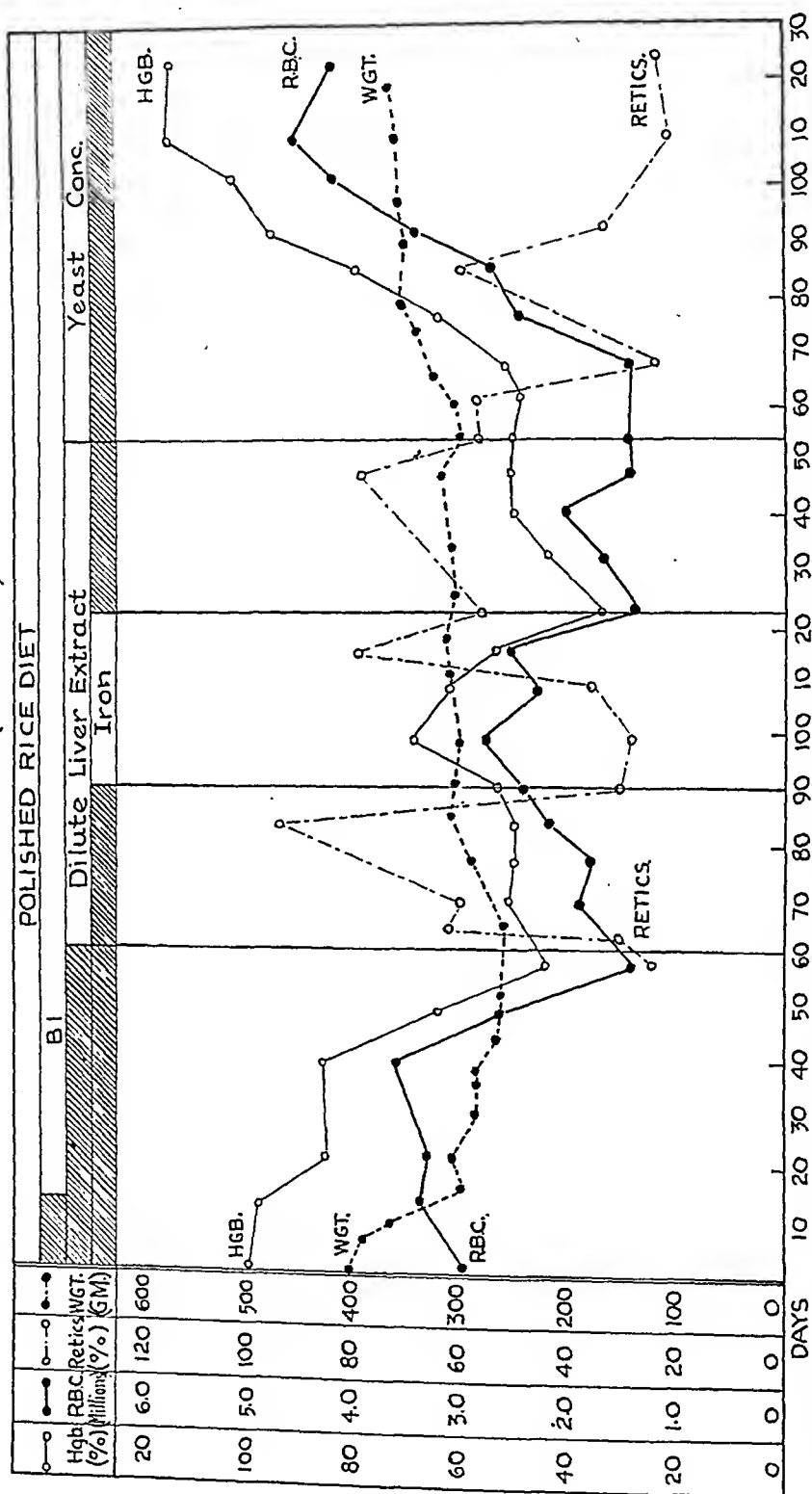


CHART VIII.—Pigeon 17. A well-marked anemia developed on a diet of polished rice with added thiamin. Administration of a dilute liver extract resulted in a marked reticulocytosis and a definite increase in red cell count. Because of the lag in hemoglobin value, iron was added by parenteral route; this resulted in a temporary increase in hemoglobin but was followed by a toxic reaction. Liver extract was continued but without effect; when yeast concentrate was then given orally, a striking response clinically and hematologically ensued.

animals. They appeared listless, stood quietly in their cage, usually with head bent on the chest. Shivering spells were often noticed. The feathers, normally clean, sleek, pure white, and closely applied to each other, became unkempt, dirty-gray, and irregularly "ruffled" or "fluffed out." As the deficiency developed, definite changes became noticeable in the beak, claws, and epidermis of the legs. The normally smooth, red appearance of these parts became lost and the epidermis developed an irregular, dirty, brownish, hyperkeratinized appearance. There was slow progression of symptoms for 3 to 6 months, and unless specific therapy was begun, death occurred usually within the 6-month period.

With development of this deficiency state, anemia gradually developed (in 17 of 20 pigeons in Series VI). A definite anemia was discernible between 28 and 90 days (average 52 days). Anemia became most marked from 41 to 107 days following the induction of the deficiency (average time 66.2 days). At this time, some sort of therapy was usually begun so that the lowest possible level of anemia which might develop was not determined. The hemoglobin at this time varied from 39 to 76% (average 58.2%), and the erythrocyte count from 1.28 to 2.69 millions (average 2.01 millions). The color index in these cases was always high, although the significance of this factor in the blood of pigeons is questionable. Estimations of the hematocrit and the mean corpuscular volume were not made. At the height of the anemia there was well-marked variation in size and shape of the red blood cells with the presence of many small "polychromatophilic" cells with deeply basophilic cytoplasm (corresponding to the presence of nucleated erythrocytes in human anemia?). The erythrocytic nuclei, normally pyknotic and situated longitudinally in the cell parallel to its long axis, not uncommonly became transversely placed. The strands of nuclear chromatin also became less well-defined (immaturity). The reticulocyte count usually increased to levels of between 20 to 30%. No particular changes in the leukocytes or thrombocytes were evident, although at times a well-marked increase in granulocytes was present. The appearance of the bone-marrow of pigeons dying of this deficiency was variable, depending in most part upon the duration of the deficiency state. Of 20 marrows examined completely, 9, from pigeons with long-standing deficiency and well-marked anemia, showed essentially the same picture. This was characterized by well-marked cellularity, the presence of many primitive cells classed as erythrogonies, and marked increase in early red blood cells.

Differential count of the bone-marrow smear in a typical case (Series V, Group XI, Pigeon 2) showed the following: Ratio of R.B.C. to W.B.C. 1:0.18. The red cells were differentiated as follows:

	Per cent.
Primitive R.B.C. (erythrogonies; normoblasts "A") . . . . .	27.2
Normoblasts "B" . . . . .	37.4
Normoblasts "C" . . . . .	21.0
Mature R.B.C. . . . .	12.4

In counting 500 R.B.C. 18 mitoses were seen.

Normal marrows in this group of B<sub>2</sub> deficiency were found when the birds were sacrificed at 9 days and 12 days respectively. After this period, and until well-marked anemia was present, the picture was variable, the marrow being either essentially normal, hypocellular, or hypercellular in appearance. Occasionally, a very marked leukocytic hyperplasia suggesting leukemia was present. In 2 birds dying suddenly during the course of this experiment, this possibility was definitely present in view of the very large spleen and the bone-marrow picture.

**EFFECTS OF VARIOUS SUBSTANCES ON THE B<sub>2</sub> DEFICIENCY STATE.**  
*Riboflavin and Riboflavin Phosphate.* In Series I, II, III, and V, 15 animals were given these substances simultaneously with the development of the deficiency and the marrows studied at death. These showed great variability from animal to animal in the same group, although there was usually a curious picture of marked hypoplasia with the presence throughout of finger-like vascular channels filled with mature red blood cells. In 3 pigeons (Series VI) given injections of riboflavin or its phosphate during the development of the B<sub>2</sub> deficiency state, there was continued and progressive clinical and hematological decline. The effect of this substance may be said to be entirely negative in these experiments.

*Nicotinic Acid.* In Series VI, 3 pigeons given injections of nicotinic acid during the course of the B<sub>2</sub> deficiency state showed a continued and progressive decline in their clinical and hematological status.

*Vitamin B<sub>6</sub>.* Crystalline vitamin B<sub>6</sub> in solution was obtained from Lepkovsky and administered parenterally to 3 deficient pigeons in Series VI. No responses either clinically or hematologically took place.

*"Filtrate Factor" (Lepkovsky).* This material, a heavy brown liquid, was obtained from Lepkovsky, and administered orally to 2 deficient pigeons in Series VI. No responses occurred.

*"Chick-dermatitis" Factor (Elvehjem).* This material, a colorless solution, was obtained from Elvehjem and administered parenterally to 2 deficient pigeons in Series VI. Although reticulocyte responses took place, there was no definite clinical improvement and no increase in erythrocytes. Further experiments with this substance are planned.

*Vitamin B Complex (parenteral, Lederle) (Series VI).* Three deficient pigeons given this material by injection showed a slow, though definite improvement in clinical and hematological status. In Pigeon 11 (Series VI), following a slight response to this medication, the administration of yeast resulted in a marked response.

*Liver extract, relatively dilute (Lilly "concentrated").* In all the 4 pigeons given this material parenterally, there was a striking response. There was rapid improvement in clinical status with marked gain in weight, reappearance of the normal alert appear-



ance, disappearance of the "fluffed out" and dirty appearance of the feathers, and replacement of the hyperkeratinized epidermis of the beak and claws by normal skin. Before the onset of clinical improvement, and within 2 to 5 days after the beginning of injections, there was an extreme reticulocytosis of 60 to 85% with the appearance of many "polychromatophilic" red cells. This picture was shortly followed by an increase in the erythrocyte count and a somewhat slower increase in the hemoglobin concentration. When iron was given to 2 animals in which hemoglobin production appeared to lag, there was a definite (temporary) increase in hemoglobin production (see under iron). Associated with the change to normality of the blood counts, there was an associated change to normality of the red blood cells in the stained preparations. In 1 animal (Series VI, No. 17) which had become very anemic after iron administration ("toxic" reaction), liver extract resulted in a marked and sustained reticulocytosis, which was, however, not followed by an increase in the red cell count. When yeast was then given orally, there was a rapid increase in the erythrocyte count.

*Liver extract*, highly concentrated (Lilly "Reticulogen"). Two pigeons with B<sub>2</sub> deficiency were given injections of "Reticulogen." There was a slow but progressive improvement in the clinical status in both, and a very slow but definite hematological response in one. In one of the pigeons (Series VI, Pigeon 14), a well-marked response occurred when injections of the relatively dilute liver extract were substituted for the concentrated material.

*Yeast*. A yeast concentrate was given by mouth to 4 pigeons with uniformly excellent results. In each instance, there were striking clinical and hematological effects. When yeast concentrate was given to a pigeon (Series VI, Pigeon 11), which had shown only a slight response to parenteral B complex, a rapid rise in both hemoglobin and red cell count took place. In another pigeon (Series VI, Pigeon 17), there was a well-marked erythrocyte response to yeast after liver extract had resulted only in reticulocytosis. Continuance of yeast therapy resulted in extremely high hemoglobin and erythrocyte levels.\*

*Iron*. A solution of iron citrate was given parenterally to 2 pigeons in which hemoglobin production following liver extract injections appeared to be lagging behind erythrocyte formation. In both instances, there was a quick rise in hemoglobin, which was, however, followed by definite toxic effects as indicated by vomiting, weakness, rapidly progressive anemia and reticulocytosis (hemolytic anemia?). These symptoms improved upon continuance of iron therapy.

**Discussion.** A. *Pigeon "Pellagra" or "Dermatitis."* The pigeon has been the classical animal used in the study of beri-beri, B<sub>1</sub>

\* The administration of yeast to normal pigeons (in a preliminary study) has resulted in definite increases in hemoglobin and erythrocyte values.

deficiency.<sup>31</sup> The response to thiamin chloride in animals made B<sub>1</sub> deficient by a diet of polished rice is a striking one and has been the subject of many publications.<sup>32</sup> Definite deficiency states relating to the various elements of the B<sub>2</sub> complex have also received much attention. At the present writing, riboflavin, nicotinic acid, and vitamin B<sub>6</sub> (the rat anti-dermatitis principle), have been isolated in pure form and their deficiency states well described. Other deficiencies in various factors of the B<sub>2</sub> complex, not so well-defined, have also been described. In 1930 "Norris and Ringrose reported the development of a pellagra-like syndrome in chicks placed on a normal diet except for the use of powdered egg-albumin in place of the more common protein of animal origin. . . . The addition of 5% of autoclaved yeast prevented the symptoms."<sup>9</sup> In 1932, Kline, Keenan, Elvehjem and Hart<sup>16</sup> produced similar symptoms in chicks ("chick-pellagra"), which were given a diet of natural food-stuffs heated dry at 95° to 100° C. for 144 hours. No symptoms developed when the diet was supplemented with 0.8% of dilute liver extract (Lilly 343). Elvehjem and his collaborators then set about the task of isolation of this "anti-pellagra" factor and soon found that flavin and the "anti-pellagra" factor must be separate substances.<sup>10</sup> The inefficacy of the flavins in both chick and human pellagra was soon demonstrated. Lepkovsky and Jukes<sup>18a</sup> almost simultaneously made much the same observations and introduced the term "filtrate factor"<sup>18c</sup> for the material which was active in the prevention and treatment of chick pellagra. For some time, Elvehjem believed that the chick pellagra factor was identical with that active in dog black tongue and in human pellagra, but his recent work<sup>11</sup> and that of others with nicotinic acid demonstrated conclusively that the latter was the deficient factor in dog black tongue and in human pellagra.<sup>26,28</sup> The chick-pellagra factor, or better the chick anti-dermatitis factor\* is thus not nicotinic acid and as yet has not been isolated in completely pure form. However, recent fractionation studies of Elvehjem and his collaborators<sup>20,35</sup> have shown considerable progress in this direction.

Thus, riboflavin, nicotinic acid (P-P factor), vitamin B<sub>6</sub> (rat anti-dermatitis principle, Factor 1 of Lepkovsky) have been isolated in pure form and their deficiencies described. Chick dermatitis and the chick anti-dermatitis principle are well along in description and isolation. Other less well-defined factors, and others perhaps undiscovered also exist in the B<sub>2</sub> complex:<sup>9</sup> Thus, Vitamin B<sub>3</sub> and Vitamin B<sub>5</sub> have respectively been described as weight-maintaining and weight-gaining factors in pigeons and Vitamin B<sub>4</sub> may be of some significance in a specific paralysis in chicks and pigeons. Reader<sup>25</sup> stated in 1929 that a tendency of the animal to sit in a hunched position was characteristic of a deficiency in this vitamin. The so-called Factor W<sup>12</sup> may also be of some importance.

\* The Committee on Vitamin Nomenclature has ruled that the term "pellagra" should be used only in cases of humans.

Our work with pigeons has demonstrated that deficiency in the entire B<sub>2</sub> complex results (1) in a clinical state resembling chick dermatitis and which may be called pigeon dermatitis; (2) in anemia characterized by reduction in both hemoglobin and erythrocyte count but particularly in the latter; and (3) failure of response of either anemia or dermatitis to riboflavin, nicotinic acid, vitamin B<sub>6</sub> (rat anti-dermatitis principle); and the "filtrate factor" of Lepkovsky; (4) striking response to dilute liver extract and to yeast and a possible response to the purified chick anti-dermatitis factor of Elvehjem. Other substances in the B<sub>2</sub> complex, namely Factors B<sub>3</sub>, B<sub>4</sub>, B<sub>5</sub>, various combinations of factors, or unknown factors may be implicated. There can be no doubt that the pigeons in these experiments were deficient in these factors, but for want of pure extracts of these substances, nothing definite can be stated regarding their relationship to the deficiency produced. The reticulocyte response with Elvehjem's chick dermatitis factor may indicate that this substance, *together with some other*, is implicated. The complete lack of response to a closely comparable substance—"filtrate factor"—is peculiar and indicates that these substances are not identical.

B. *Pigeon Anemia*. It is evident that a definite anemia develops in pigeons kept on a diet of polished rice supplemented with injections of thiamin chloride. This anemia is compatible with life over a period of several months and is not simply a terminal event. Indicative of the fact that it is primarily due to a deficiency and not to other unrecognized factors are: (1) its gradual development as the deficiency progresses; (2) the hyperplastic appearance of the marrow with "maturation arrest," quite typical of a deficiency state; (3) the well-marked reticulocytosis (and erythrocytosis) which result when the deficient substance is added to the diet; and (4) the gradual improvement in the clinical status of the affected pigeons.

The development of anemia in pigeons on deficient diets has had some previous study. Muller<sup>23</sup> studied the effects of various substances during recovery from the marked anemia and inanition produced by a period of complete starvation for 7 to 13 days. A mixed grain diet and broiled beef muscle contained elements which allowed complete recovery. The use of broiled beef liver, after an initial recovery of the red cell and hemoglobin levels was associated with an exacerbation of anemia, and later anorexia and marked weight loss. Liver after water extraction was without effect on the anemia of starvation, but liver after dilute alcohol extraction caused a complete remission. Muller ascribed this to the removal of some inhibiting factor present in liver, although it is possible that the lack of effect after water extraction might have been due to the loss of various factors of the B<sub>2</sub> complex present in liver and soluble in water.

Barlow,<sup>2</sup> also using the starvation technique, found that grain

and beef muscle caused improvement of anemia in most cases. Cooked or raw beef liver were without effect; however, when beef muscle and beef liver were both given, the anemia improved. Barlow also found that a diet of polished rice or a synthetic diet deficient in Vitamin B factors produced an anemia. This anemia was prevented and cured by Harris's yeast extract, but not by the Lilly liver extract 343 (Fraction G of Cohn). He attributed the ineffectiveness of liver to its deficiency in certain factors of the B vitamin.

Hogan, Richardson, and Johnson,<sup>15</sup> after producing beri-beri in pigeons by a deficient diet, gave large doses of concentrated Vitamin B<sub>1</sub>. Within 1 week, recovery from polyneuritis had occurred, but a severe anemia was present with a red cell level below one million. This anemia yielded to a low calorie diet adequate in vitamins, but did not respond to flavin or the anti-dermatitis principle(s).

The anemias produced by Muller and Barlow are hardly comparable with the type produced in our experiments. The rapid onset of the anemia and the marked inanition are indicative of multiple deficiencies. In Barlow's experiments with a diet of polished rice without added B<sub>1</sub> the lack of the latter factor might well have led to changes in the gastro-intestinal tract, the liver, and the bone-marrow long before the changes due to deficiency in the B<sub>2</sub> complex could occur. The work of Hogan *et al.* is somewhat more similar to our own, but here again the preliminary depletion of B<sub>1</sub> might conceivably promote changes initiating the rapid onset of anemia.

*C. Anemias With B<sub>2</sub> Complex Deficiency in Other Species Than Pigeon.* It is hazardous to compare deficiencies of one species with those of another. In the first place, deficiencies of one fraction of B<sub>2</sub> complex may produce pathologic changes in one species and not in another; *e. g.*, rats do not require nicotinic acid,<sup>5</sup> the lack of which produces black tongue in dogs and pellagra in man. In more closely related species this is also true. Lack of riboflavin does not produce dermatitis in chickens but does so in turkeys.<sup>18b</sup> In the second place, the same symptom in different species may be due to deprivation of different factors in the B<sub>2</sub> complex. Thus, rat dermatitis is cured by B<sub>6</sub>, a fraction of yeast which is absorbed by fuller's earth, whereas chick dermatitis is not affected by B<sub>6</sub> but is relieved by "filtrate factor," the filtrate resulting from removal of the above adsorbate. Finally, the diets described have differed in other particulars besides those of the known vitamins. For example, lack of certain fatty acids will cause rat dermatitis despite the presence of B<sub>6</sub>.<sup>4</sup>

Anemia from a deficiency in various fractions of the B vitamin has been described in dogs, monkeys, swine, rats, and chickens.

*Dogs.* Miller and Rhoads<sup>21</sup> fed a pellagra-producing diet (deficient in Goldberger's P-P factor but not in B<sub>6</sub>) and obtained a macrocytic anemia with megaloblastic bone-marrow. There was no improvement with liver extract; but complete recovery occurred with beef.

Spies,<sup>27</sup> with a similar diet, produced anemia which was prevented by ventriculin and cured with yeast.

Birch, György, and Harris<sup>5</sup> produced anemia with a diet containing B<sub>6</sub>, but not P-P or lactoflavin. This anemia responded to fish (which has no lactoflavin) and to the Lilly liver extract 343 (which has no B<sub>6</sub>), *i. e.*, the anemia was due to some other factor of the B<sub>2</sub> complex.

Fouts *et al.*<sup>13</sup> fed puppies a diet deficient in B<sub>6</sub> but containing casein, B<sub>1</sub>, riboflavin, and filtrate factor. The anemia which developed responded by a reticulocyte crisis and increase in red cell and hemoglobin levels to purified, and later, crystalline vitamin B<sub>6</sub>.

*Monkeys.* Day *et al.*,<sup>8</sup> using a modified Goldberger diet, produced anemia which was prevented by brewer's yeast.

Wills *et al.*,<sup>33</sup> using a similar diet, produced anemia which responded to "marmite" and liver extract. Liver extract was divided into two factors, one soluble in (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and the other insoluble. The soluble fraction was usually effective in both pernicious anemia and the deficiency anemia in monkeys, although an occasional monkey required both fractions. The insoluble fraction was effective in pernicious anemia but without effect in monkey anemia. This anti-anemia factor for monkeys was present in yeast, marmite, and wheat germ. They make the statement, although they give no evidence, that this factor is neither B<sub>6</sub> nor the filtrate factor.

*Rats.* Sure, Kik, and Smith<sup>29</sup> fed rats a diet deficient in the vitamin B complex plus 500 mg. (daily) of rice polishings irradiated for 10 hours to destroy vitamin G. Some animals tended to less weight, while others developed a dermatitis. There was a much higher correlation of anemia with dermatitis than with weight loss.

Guha and Mapson<sup>14</sup> produced anemia on a basal diet supplemented by B<sub>1</sub>. Autoclaved liver extract, as well as autoclaved marmite, corrected this.

Manville and Grondahl<sup>19</sup> placed their animals on a basal B free diet supplemented with varying amounts of yeast. After anemia developed, the animals were placed in a low pressure chamber. They found that with the higher percentages of yeast, the low pressure had a greater effect in stimulating the bone-marrow. Apparently some factor in yeast was necessary for the development of "megaloblasts" to normoblasts.

Bethell and Sturgis,<sup>3</sup> using a milk diet, produced a macrocytic anemia which responded to vitamin B<sub>1</sub>. This article is published in abstract form and further details are lacking.

*Swine.* Miller and Rhoads<sup>21</sup> produced anemia in swine on a dog black tongue diet. Some of the animals developed a macrocytic type of anemia while others developed a microcytic form. The bone-marrow was hyperplastic and megaloblastic. Both types of anemia responded to Lilly's liver extract 343 (Fraction G). Control animals on Vegex or egg white developed no symptoms except achlorhydria. Egg white is deficient in both B<sub>6</sub> and in the anti-chick dermatitis factor (F. F.).

*Chickens.* With chickens fed on the Koehn-Elvehjem diet, Birch, György, and Harris<sup>5</sup> believed that these animals became anemic "as judged by the striking pale condition of their combs." When the maize, middlings, and extracted caseinogen were not heated, anemia did not develop. Yeast was ineffective in preventing the anemia.

**Comment.** Although these investigations with deficient diets in various animals present certain discrepancies and inconsistencies, in general they show the same trend. The inconsistencies are in all probability due, not only to species variations, but to the difficulties inherent in preparing exactly comparable diets. Furthermore, until very recently, the various factors had not been available in

sufficiently pure form to make one certain of the nature of the specific agent responsible for a therapeutic result. The situation in regard to recognition and purification of the various factors of the B<sub>2</sub> complex shows such rapid change that a publication of even a year ago is by now outdated. In the last 2 years alone, nicotinic acid has been recognized as the P-P factor, vitamin B<sub>6</sub> has been isolated in crystalline form, and the chick anti-dermatitis factor of Elvehjem has been stated to be pantothenic acid.<sup>35</sup> Although experimentation is naturally rendered more exact by the use of pure substances, certain complexities are, however, introduced because of the possibility that *combinations of pure substances* may be necessary for a given effect. Several substances are still present in the B<sub>2</sub> complex which (until today) have not been isolated in pure form: Vitamins B<sub>3</sub>, B<sub>4</sub>, B<sub>5</sub>, W factor. Still other factors, whose physiologic effects have not even been recognized, are undoubtedly present in yeast and liver.

In the present state of our knowledge we can state quite definitely that a diet deficient in vitamin B produces a deficiency state usually accompanied with anemia in a variety of animals: pigeons, dogs, monkeys, rats, chicks, and swine. This anemia has responded in most instances to crude liver extract and to yeast. Little progress has thus far been made in elucidating which of the numerous factors in these substances is responsible for the anemia. Our investigations definitely exclude vitamin B<sub>1</sub>, riboflavin, nicotinic acid, vitamin B<sub>6</sub>, and in all probability the filtrate factor of Lepkovsky. Since the anemia in our cases was not microcytic and did not respond to B<sub>6</sub>, it must differ from the hypochromic anemia produced by Fouts *et al.* in puppies. The reticulocytosis which occurred following the injection of the purified chick anti-dermatitis principle of Elvehjem may indicate that this factor is at least partially responsible for the anemia. Isolation of another factor or co-factor must await further investigation.

The findings in the bone-marrow of hyperplasia and immaturity ("maturation arrest"), the hematological findings, and the development of a reticulocyte crisis and erythrocyte response when effective substances were given resemble those seen in the "liver extract" deficiency state of humans known as "pernicious anemia."<sup>7</sup> The changes in the feathers and epidermis are perhaps comparable to such clinical phenomena in pernicious anemia as greying of the hair, baldness of the tongue, and so on. These similarities may indicate a possible relationship between the experimental pigeon dermatitis and the human disease. Pernicious anemia has been amply demonstrated to be a deficiency disease. The exact type of deficiency which is present has thus far not been elucidated, although the B<sub>2</sub> complex may be involved. In most instances this deficiency is "conditioned," as Castle has pointed out, by a gastric abnormality. In many cases, however, an inadequate diet together with a gastrointestinal defect, is responsible for the development of the syndrome.

Some cases in which the dietary factor is outstanding will respond simply to a diet rich in protein substances and containing vitamin B in excess.<sup>1</sup> Wintrobe's experiments with yeast and yeast products indicate that yeast alone is frequently effective in the therapy of pernicious anemia.<sup>34</sup> This may indicate either (1) that Castle's enzyme is not a prerequisite for the final elaboration of "liver extract-substance;" (2) that yeast, when given in excess, contains so much "extrinsic factor" that is sufficient even with the small amount of "intrinsic factor" probably present, to initiate a response; or (3) that both yeast and liver extract contain quite similar factor(s).

Our studies, which demonstrate that both dilute liver extract and yeast concentrate are effective in pigeon B<sub>2</sub> complex deficiency anemia bring the problem to about the same stage. The anti-pernicious anemia principle was apparently not of itself entirely effective in our anemia. Thus, in one pigeon, although a well-marked reticulocytosis ensued with dilute liver extract, no rise in erythrocytes occurred until yeast was given. In several other pigeons, highly concentrated liver extracts, containing presumably anti-P.A. principle in excess, and with but little vitamin B complex, caused a slow, rather ineffective response as compared with that of yeast. For these reasons, it is apparent that, although pigeon dermatitis and pernicious anemia have certain points of resemblance they are probably not due to the same type of deficiency.

The various attempts to use normal pigeons as assay animals in testing liver extracts<sup>22,30</sup> are probably invalidated, since the results which have occurred are probably due to a factor or factors in the B<sub>2</sub> complex and not to the anti-P.A. principle itself. Whether the latter will eventually be shown to be one of the numerous substances present in the B<sub>2</sub> complex remains to be seen. At any rate, the complexities of liver extract and of yeast offer a continued challenge to investigators in chemical, biological, and clinical fields.

**Summary and Conclusions.** 1. Pigeons on a diet of polished rice with added vitamin B<sub>1</sub> (thiamin chloride) parenterally developed a deficiency state (pigeon dermatitis) characterized by: 1, loss of weight, changes in the feathers and epidermis; and, 2, progressive anemia associated with a hyperplastic, immature marrow.

2. This deficiency state did not respond to riboflavin, nicotinic acid, vitamin B<sub>6</sub>, or filtrate factor (Lepkovsky).

3. Striking clinical and hematological responses occurred with yeast concentrate, dilute (parenteral) liver extract, and (parenteral) B<sub>2</sub> complex. Concentrated liver extracts gave either a partial or a delayed response. Elvehjem's purified chick-anti-dermatitis principle resulted in a definite reticulocyte response which was, however, not followed by an erythrocyte increase.

4. Pigeon dermatitis is due to a deficiency in a factor or factors in the vitamin B<sub>2</sub> complex. This factor does not appear to be riboflavin, nicotinic acid, or vitamin B<sub>6</sub>. It is probably not identical with the liver-extract-principle effective in pernicious anemia.

The chick anti-dermatitis principle, either alone, or in association with some unknown factor, may be the vitamin which is responsible for the deficiency state.

5. The findings in the bone-marrow and the striking hematological responses to yeast and dilute liver extract resemble those seen in the "liver extract" deficiency state of humans (pernicious anemia). Whether this indicates a possible relationship between pigeon dermatitis and pernicious anemia is problematical. At any rate, the complexities of yeast, the B<sub>2</sub> complex and liver extract continue as outstanding challenges to investigators in numerous fields.

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## FOCI OF INFECTION IN PSYCHIATRIC PATIENTS.

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THE causal relationship of foci of infection to general systemic diseases was recognized by Benjamin Rush<sup>5d</sup> in 1819 in a case of arthritis which recovered after removal of dental infection. It



was not until 1912, however, that attention to foci of infection was greatly stressed, by Billings,<sup>2a</sup> Roscnow, Jackson and others. In 1912, Gilmer<sup>3</sup> raised the question of the importance of the effect of dental foci of infection—alveolar abscesses and pyorrhea—on the general health of the individual. In 1913, Billings,<sup>2b</sup> studying 70 cases of arthritis deformans, concluded, "Focal disease was usually located in the head. Chronic alveolar abscess and chronic sinusitis due to streptococci were an occasional cause. Most frequent was chronic streptococcic focus of faucial tonsils. Occasionally the focus may be in the prostate gland, seminal vesicles, female genitalia and probably also in a streptococcic chronic appendicitis or a circumscribed streptococcic infection anywhere." Young,<sup>8</sup> in the same year, states, "In conclusion, I may say that the prostate and seminal vesicles are very frequently the site of chronic inflammatory processes which often continue for years, give very few local symptoms and are the insidious cause of remote processes. This fact should bring home to all practitioners of medicine the very great importance of rectal examinations as a routine procedure."

In the ensuing years the importance of foci of infection as a cause of systemic disease has been much debated, widely studied and variously evaluated (Pemberton,<sup>5a,c,d,s</sup> Biering<sup>1</sup>).

While there have been a great number of articles and work relating the presence of foci of infection to such systemic diseases as arthritis, there have been few studies that show the incidence of foci of infection in physically well human beings. An attempt at such a study was made by Pemberton<sup>5b</sup> when he studied 100 consecutive hospital admissions for foci of infection. In this series of cases foci of infection were present in 87% of the cases, a higher incidence than the same worker obtained in arthritic patients. A just criticism of this work is that these patients were not physically well, and hence one might expect a higher incidence of foci of infection than in a group of physically normal people.

It is the purpose of the present study to determine the incidence of foci of infection in a group of patients who are apparently physically well. The group of patients we elected to study are a group of psychotic patients at this hospital who were hospitalized because of mental rather than physical sickness. There is no reason to expect in a group of mentally sick but apparently physically well patients any difference in incidence of foci of infection than would obtain in a similar economic and geographic group of physically normal human beings.

Patients on the psychiatric service at this hospital routinely have examinations for foci of infection, whether or not the routine physical examinations reveal or suggest the presence of a focus of infection. These routine "foci checks" usually involve nose and throat, dental, urology, gynecology, and sometimes cardiorespiratory

examinations by specialists in those fields. Further examinations, such as sinus washings, sinus Roentgen rays, electrocardiograms, chest films, and so on, are done if foci of infection are suggested by the routine checks. Since these examinations are routinely obtained, we believe the incidence of foci of infection in our group approximates the incidence in a similar economic and geographic group of physically normal humans.

TABLE 1.—FOCI OF INFECTION BY DISEASE GROUPS.

	Schizo- phrenic.	Manic- depress.	Meno- pausal.	Senile.	Paresis.	Alcoholic.	Total.
Male . . . . .	43	15	0	4	47	34	143
Female . . . . .	39	14	24	7	3	.9	96
Total . . . . .	82	29	24	11	50	43	239
Average age . . . . .	27.5	39.1	42.7	66.1	43.9	42.5	38.9
Incidence of foci of infection . . . . .	59%	55%	65%	80%	68%	62%	62.8%

From Table 1 we see that the incidence of foci of infection for our entire group is 62.8%, a figure slightly lower than the incidence of foci of infection Pemberton found in 1100 arthritic patients (70%),<sup>5a,d,6</sup> or in a group of 100 consecutive hospital admissions (87%).<sup>5b</sup>

Though 62.8% of our cases had foci of infection, none of them had arthritis and only 2 had rheumatic heart disease, both diseases widely thought to be caused by foci of infection. It is obvious then, since our patients with foci of infection did not develop arthritis or rheumatic heart disease, that there must be some other physical condition present in patients who do develop arthritis from foci of infection. It has been suggested that the arthritic patient is allergic to the bacteria present in his focus of infection or that he has a constitutional predisposition to joint involvement. Pemberton and Pierce<sup>6</sup> found hereditary influences in 58% of 1100 arthritic patients, and later Pemberton states,<sup>5d</sup> "The proverbial relation of soil and seed is here exemplified, the soil being afforded by the constitutional background, the almost necessary predisposing cause; the seed being represented by infection or some other factor, the frequently exciting agent."

• There is a lower incidence of focal infection in our series than in a group of 100 consecutive hospital admissions which were evidently admitted to the hospital because of physical ailments (cardiorespiratory conditions, nephritis, arthritis, and so on). We believe that one can, of course, expect a higher incidence of foci of infection in the physically ill patient. From the above table it is also evident that there is little difference in incidence of foci of infection by disease group or by the age of each disease group.

TABLE 2.—FOCI OF INFECTION BY NUMBER OF FOCI EXAMINATIONS.

Number of foci checks.	Number of patients.	% having one focus of infection.	% having more than one focus of infection.
None . . . . .	23	0	0
One . . . . .	14	40	0
Two . . . . .	42	40	14
Three . . . . .	89	68	19
Four . . . . .	71	75	37
	239		

From Table 2 we see that the majority of our patients had a minimum of 3 foci examinations (160 out of 239), while 202 out of 239 had at least 2 foci checks. Unfortunately, the mental condition present in our type of patient made foci checks difficult or sometimes impossible. A further circumstance that made it impossible for all the patients to receive all the examinations was that some left the hospital before the studies could be completed.

Table 2 shows that with the greater number of checks the known incidence of focal infection rises—40% in the group that had 1 and 2 checks, and 75% in the group that had 4 checks. An axiom of modern medicine that this confirms is simply that the known incidence of focal infection in any group of patients is in direct proportion to the thoroughness with which the patients are examined for such foci.

It would seem probable that if our entire group had the 4 foci examinations the incidence of focal infection in our entire series would approximate 75%. This compares favorably with the incidence of focal infection (70%) Pemberton found in 1100 arthritic patients. Consequently it is evident that the incidence of focal infection is approximately the same in a group of arthritic patients as in a group of apparently physically normal patients.

TABLE 3.—FOCI OF INFECTION BY SYSTEMS.

	Nose-throat.	Dental.	Urol.	Gynec.	Cardio-resp.
Number of cases checked for foci . . . . .	180	174	100	67	125
Foci present . . . . .	80	65	17	15	13
Per cent of cases checked having foci present . . . . .	44	37	17	22	2.4
Per cent of cases checked having other pathologic conditions present . . . . .	22	29	1	21	66.8

From Table 3 we see that the most common site for a focus of infection is in the nose and throat, which agrees with the early work by Billings.<sup>2a,b</sup> In Pemberton's<sup>5b</sup> study of 100 consecutive hospital admissions, he found the dental and nose and throat foci of infection to be about the same in incidence (58% and 56%). Dental foci of infection were present in a little over one-third of our patients, while two-thirds of our patients needed dental treatment. The next most common focus of infection lay in the genito-urinary tract

(22% and 17%) in our study. True foci of infection were rare in the cardiorespiratory system, being present in only 1.6% of our patients. However, such conditions as luetic heart disease, rheumatic heart disease, hypertension and arteriosclerosis, which were relatively common, were not considered foci of infection.

TABLE 4.—NATURE OF PATHOLOGIC CONDITIONS IN THE NOSE AND THROAT.

	Cases.	% of cases checked.
Foci present:		
Chronic tonsillitis—adenoids	39	22
Sinusitis	36	20
Maxillary		
Ethmoid	15	
Frontal	4	
Otitis media	0.6	
Mastoiditis, acute rhinitis and pharyngitis	3	
Atrophic rhinitis and ext. otitis	2 each	
Laryngitis	1 each	
Other pathologic conditions:		
Deviated septum	0.6	
Tonsillar tags	12	
Perforated septum, polypi, nerve deaf	4	

From Table 4 we see that by far the two most common causes of foci of infection in the nose and throat are chronic tonsillitis and sinus infection. The diagnosis of sinus infection was based on transillumination, sinus washings, and Roentgen ray findings. Other causes of foci in the nose and throat are relatively uncommon. There are no distinctive differences in the focus of infection in the nose and throat in our different disease groups (schizophrenic, manic-depressive, and so on).

TABLE 5.—PATHOLOGIC DENTAL CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Alveolar or apical abscesses in dead, carious teeth or root fragments	53	30
Pyorrhea	27	15
Gingivitis	4	2
Other pathologic conditions:		
Caries	63	36
Dead teeth (not infected)	12	7
Calcareous deposits	4	2
Impacted molars	8	5
Cyst	1	0.5
Leukoplakia	1	0.5

From Table 5 it is clear that the most common foci of infection in the mouth are in apical or alveolar abscesses in dead, or carious teeth, or in root fragments (30%). The diagnosis of apical abscess was based on dental examinations and Roentgen rays. The next most common focus of infection in the mouth was pyorrhea (15%). It is striking that two-thirds of our patients needed dental attention of some sort, and that 36% of our group had dental caries. There are no striking differences between our different disease groups.

Urologic foci of infection were found to be present in 17% of the 100 cases examined; 16% had chronic prostatitis, 2% non-specific urethritis and 1% cryptitis. Of our parietic patients 33% had a focus of infection in the genito-urinary tract, while only 10% of all our other cases had such an infection. We believe this to be entirely logical because there is a high probability that the man who contracts syphilis will also contract a Neisserian infection with the resultant chronic prostatitis developing in later years. One patient had a malignant kidney tumor.

TABLE 6.—PATHOLOGIC GYNECOLOGIC CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Chronic cervicitis . . . . .	12	18
Salpingitis . . . . .	2	3
Trichomonas . . . . .	1	1.5
Other conditions:		
Fibroids . . . . .	3	4.5
Labial cysts . . . . .	3	4.5
Rectocele and cystocele . . . . .	2	3 each
Kraurosis vulvæ, polyp, pregnancy, descensus uteri, and so forth . . . . .	1	1.5 each

Table 6 shows that chronic cervicitis is relatively common in women; other foci of infection are relatively uncommon.

TABLE 7.—CARDIORESPIRATORY CONDITIONS.

	Cases.	% of cases checked.
Foci present:		
Bronchitis . . . . .	2	1.6
Other conditions:		
Arteriosclerosis . . . . .	16	12.8
Hypertension . . . . .	8	6.4
Luetic heart disease or aortitis . . . . .	8	6.4
Coronary sclerosis . . . . .	3	2.4
Angina and rheumatic heart disease . . . . .	2 each	1.6 each
Tuberculosis . . . . .	1	0.8

From Table 7 we see that the incidence of foci of infection is very low in the chest. However, other conditions are relatively common, arteriosclerosis being present in 12.8% of our cases and hypertension in 6.4%. Our incidence of luetic heart disease is undoubtedly not the normal incidence, because of the inclusion in our group of 50 parietic cases. It is noteworthy that 17% of our parietic cases, when checked by the heart specialist, Roentgen ray, and the electrocardiogram, had signs of syphilitic involvement of the heart or the aorta. Morgan<sup>4</sup> states that from 10 to 15% of acute untreated cases of syphilis developed cardiovascular syphilis. It is obvious, with 17% of our cases of neurosyphilis developing cardiovascular syphilis, that the development of neurosyphilis confers no immunity at all against the development of cardiovascular syphilis.

The above figure of 17% of our parietic patients developing cardiovascular syphilis certainly indicates the necessity of a careful heart

examination before any fever therapy is attempted in a paretic patient, although Stokes<sup>7</sup> states that the paretic patient with cardiovascular syphilis can often be carefully coaxed through two short sieges of malaria. Jauregg (quoted by Stokes) believes, however, that vascular syphilis in patients with paresis is often made worse rather than better by malaria. Be that as it may, it is certainly necessary, with the high incidence of cardiovascular syphilis in paretics, that every paretic patient have a very careful cardiovascular check before any fever therapy is attempted.

**Summary and Conclusions.** Two hundred and thirty-nine patients who were hospitalized because of mental rather than physical illness were studied for foci of infection. Of these cases, 62.8% had foci of infection present.

It is obvious, with the high incidence of foci of infection in physically normal patients, that every patient should have a very careful examination for foci of infection.

Since 62.8% of our group of patients had foci of infection without developing arthritis, it is evident that other conditions must be present in the arthritic patient than just a focus of infection. It has been suggested that the arthritic patient is allergic to the bacteria present or that there is some constitutional hereditary predisposition to arthritis.

The incidence of foci of infection found in any group of patients is directly proportional to the thoroughness with which such patients are examined for foci of infection.

The most common sites of foci of infection in our study were the nose and throat (44%), dental (37%), gynecologic (22%), urologic (17%), and cardiorespiratory (1.6%). The most common nose and throat infection were chronic tonsillitis and chronic sinusitis. The most common dental infections were apical abscesses and pyorrhea. The most common urologic focus of infection was chronic prostatitis, which appears to be more common in paretic patients (33%) than in other patients (10%). The most common focus of infection in the female genitalia was chronic cervicitis.

Foci of infection in the chest are rare, yet other conditions are not uncommon. Of our paretic patients, 17% had cardiovascular syphilis, a fact that indicates the necessity of examining every paretic patient very carefully for cardiovascular involvement before they are treated with fever therapy.

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## ADIE'S SYNDROME.

## A NON-LUETIC DISEASE SIMULATING TABES DORSALIS\*

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IN 1931 W. J. Adie<sup>1a</sup> presented 5 cases illustrating a syndrome which was frequently diagnosed as tabes but was not tabes. This syndrome was characterized by the tonic pupil and the loss of one or more deep reflexes. These symptoms are chronic. They do not get worse or get better and they are not due to syphilis.

In 1932 Adie<sup>1b</sup> enlarged this syndrome to include typical and atypical types. The typical case shows an unilateral tonic pupil and one or more absent deep reflexes. These signs remain stationary, do not otherwise impair the patient's health and tend to occur in younger people, more frequently in females than in males in a ratio of about 5:1.

The atypical cases are classified: 1, tonic pupil alone; 2, atypical phases of the tonic pupil alone; 3, atypical phases of the tonic pupil with absent deep reflexes; 4, absent deep reflexes, without pupillary changes.

The typical tonic pupil may be tonic to both light and in accommodation, but most frequently is fixed to light, dilates slightly in the dark and reacts tonically in accommodation. The tonic reaction is characterized by the slow response to the stimulus usually with a latent period or delay before the response begins to take place. Moore<sup>32a,b</sup> states that one case showed a delay of 5 minutes before the reaction in accommodation began. The tonic pupil contracts very slowly and may eventually become smaller than the normal. When the stimulus is removed it may continue to contract (rare), may remain stationary for several seconds (the rule), or may proceed to dilate at once (common), dilation once begun tends to proceed at a rate even slower than that of the preceding contraction, and many seconds, or even minutes elapse before it regains its usual resting size.

A typical tonic pupil is larger than normal and unilateral; but it is subject to sudden variations in size, sometimes concomitantly with emotional stress. It is regular in outline. It dilates well with mydriatics and contracts with eserine. Repetition does not facili-

\* Read before the American Neurological Association, June 7, 1939, at Atlantic City, N. J.

tate the movement as it does in myotonia of skeletal muscle and the tonic quality is unaffected by the administration of quinine.

An atypical tonic pupil may be bilateral. It may be smaller or of the same size as the affected pupil and may be oval in either the vertical or horizontal diameters. There may be a tonic pupil on one side and a fixed pupil on the other. Adie includes certain cases of a fixed pupil, iridoplegia or ophthalmoplegia interna in this group. Hippus has frequently been reported in association with the tonic pupil.

The loss of deep reflexes is typically confined to the ankle jerks and is most often unilateral. Adie states that the arm jerks have never\* been lost in any of his patients, and that he has never seen an absent knee jerk unless the ankle jerk on the same side is also absent. Furthermore, these cases never show ataxia or sensory changes.

We are presenting 7 cases of Adie's syndrome. Moving pictures of the characteristic signs in these cases have been taken by Dr. Maurice Frocht. Stills from these moving pictures are used as illustrations in this article.

**Case Abstracts.** CASE 1.—A 32-year-old married white woman, had a dilated right pupil which was fixed to light but gave the typical tonic reaction in accommodation. The deep reflexes were normal.

Suddenly on September 1, 1936, this patient noticed a blurring of vision in her right eye. She consulted her physician that same day who made the note that the right pupil was dilated, fixed to light and reacted slowly in accommodation. Aside from this, her physical examination was normal. Roentgen ray examination of the sinuses and cervical spine were reported normal. The blood Wassermann reaction was negative on 3 occasions. The spinal fluid examination and the spinal Wassermann reaction were negative.

In spite of these negative findings, this patient was given a course of anti-luetic therapy. In the Fall of 1937 this patient was seen by Dr. W. Guernsey Frey at the Eye Clinic at St. Luke's Hospital (No. 38279). Dr. Frey made the diagnosis of Adie's syndrome and has very kindly allowed me to include this case in this series.

The pupils in this case are typical of the Adie's syndrome. The case is atypical in that there are no reflex changes.

CASE 2. A married white woman of 28, had a dilated left pupil which did not react to light but showed the typical myotonic reaction in accommodation and an absent left ankle jerk. She also suffered from convulsive seizures, diagnosed at the Neurological Institute as idiopathic grand and petit mal.

This patient reported to the Vanderbilt Clinic (No. 544153) on March 7, 1938, because of her convulsive attacks which she had had for 12 years. She had no previous knowledge that one pupil was larger than the other and had never noticed any difficulty with vision. She entered the Neurological Institute for study March 10, 1938, and was discharged March 26, 1938, with the following diagnoses; (1) idiopathic grand and petit mal; (2) pregnancy 2 to 3 months' duration; (3) Adie's syndrome. The left pupil was larger than the right, regular in outline. It did not react to light but reacted very slowly in accommodation, eventually approximating the

\* Two cases reported by Kennedy in a series of 5 were said to show absence of all deep reflexes.



right pupil in size. On ceasing to accommodate, the left pupil returned very slowly to its former size. The left pupil dilated slowly in the dark. The consensual light reflex was present from left to right, but not from right to left. One drop of 1% eserine in each eye produced a contraction of each pupil to about 1 mm. in diameter. Intramuscular injection of prostigmin increased slightly the speed of reaction of the left pupil to accommodation but did not otherwise affect it. Ten grains of quinine hydrochloride by mouth produced no change in the pupillary reaction. The left ankle jerk was absent.



FIG. 1



FIG. 2



FIG. 3



FIG. 4

FIG. 1.—Case 1. The pupils at rest.

FIG. 2.—Case 1. The reaction of the left pupil to light.

FIG. 3.—Case 1. The reaction of the right pupil to light.

FIG. 4.—Case 1. The reactions of both pupils to accommodation-convergence. It took approximately 2 minutes for the left pupil to contract in accommodation and approximately 3 minutes for it to return to its resting size after the action in accommodation ceased.

Careful laboratory studies, including the blood count, analysis of the urine, blood sugar, urea-nitrogen, glucose tolerance, and spinal fluid examinations were all normal. The Wassermann reaction on the blood and spinal fluid was negative in all dilutions. Roentgen ray of the skull showed no abnormalities. The encephalogram was reported by Dr. Dyke as showing mild cerebral and cerebellar hypoplasia or atrophy. The Aschheim-Zondek test was positive.

*Course.*—This patient's pregnancy was normal and her child was born in October, 1938. She is still under treatment in the Vanderbilt Clinic for her convulsive disorder. The pupillary findings are unchanged and the left ankle jerk is still absent.

CASE 3.\* A Puerto-Rican of 51, presented a dilated right pupil which did not react to light or in accommodation and an absent right ankle jerk.

This man was admitted to St. Luke's Hospital (No. 42001) for the first time on October 6, 1937, complaining of pains in various parts of the body. Because of language difficulty his history was difficult to obtain. He reports having had a sore on his penis in 1902 which cleared up in a few weeks with local treatment. In 1912 he first noticed that his right pupil was larger than the left. Aside from the difference in size of the pupils, he had no



FIG. 5

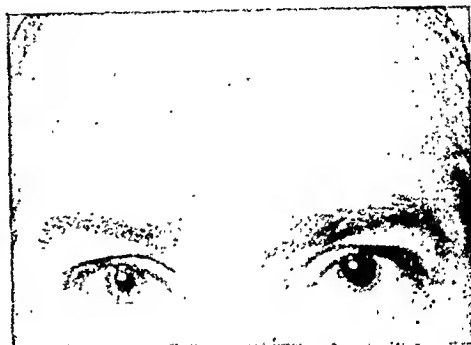


FIG. 6

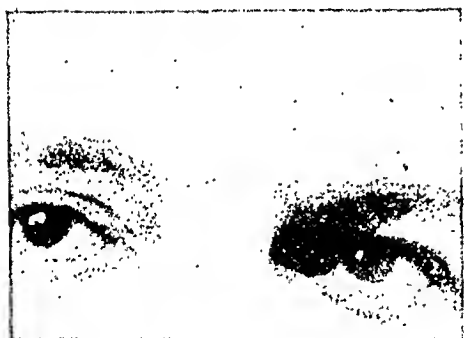


FIG. 7

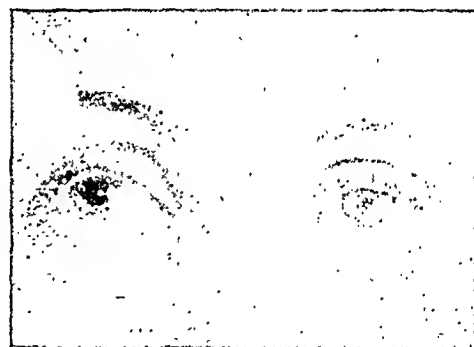


FIG. 8

FIG. 5.—Case 2. The dilated right pupil which did not react to light but reacted tonically in accommodation.

FIG. 6.—Case 3. The dilated left pupil which did not react to light and reacted very slightly in accommodation.

FIG. 7.—Case 4. The dilated left pupil which reacted imperfectly to light and tonically in accommodation.

FIG. 8.—Case 7. The dilated right pupil which did not react to light and reacted tonically in accommodation.

symptoms at this time. In 1917 he developed a rash which was fairly generalized and itching. He was told that his Wassermann reaction was 1+ and he was given 6 injections in the vein of his arm and 10 injections in the buttocks.

The neurologic examination showed the right pupil to be large, regular and fixed to light and in accommodation. The right ankle jerk was absent. There was diminished hearing in the left ear of the middle ear type and the

\* These first 3 cases were presented before the New York Neurological Society, April 5, 1939.

tonsils were enlarged and infected. Laboratory tests including analysis of the urine, blood count, blood sugar, and spinal fluid were normal. Kline and Wassermann tests were negative on both the blood and spinal fluid.

This patient's pains were thought to be due to arthritis. He was readmitted to the hospital in May, 1938, for a tonsillectomy. His blood and spinal fluid Wassermann reactions were repeated at this time and were negative. Again on a subsequent admission in February, 1939, for an attack of asthma the blood Kline test was reported negative. When last seen in May, 1939, the neurologic status was the same as reported above.

Now 51 years of age, he first noticed the enlargement of the right pupil in 1912 at the age of 24. It is unilateral and has persisted for 27 years. The right ankle jerk is absent and his serology has been repeatedly negative. In spite of the history of a 1+ Wassermann and a series of injections in 1917 we believe that this patient is an atypical case of Adie's syndrome.

CASE 4. A 40-year-old business man, showed a dilated left pupil which did not react to light and reacted tonically in accommodation. Both ankle jerks were absent and the left knee jerk could not be obtained.

In December, 1927, at the age of 27 this patient first noticed that the left pupil was larger than the right. His attention was called to this by the sudden onset of blurring of vision and an increased sensitivity of his eyes to bright lights. He was carefully examined by his family doctor at this time and in February, 1928, he was seen by Dr. George Hyslop, who made the following note: "The left pupil did not react to light and was slightly irregular. I noticed after a moment or two, the left pupil would spontaneously reduce in size. There seemed to be at times a delay in contraction to accommodation. The neurologic examination was otherwise negative save for difficulty in obtaining the knee and ankle jerks." The Wassermann reaction on the blood and spinal fluid was negative.

After 6 years observation, in 1934 the following note was made by Dr. Hyslop. "The right pupil at first was slightly larger than the left, showed a paradoxical response to direct light. The left pupil showed no reaction to light. A few moments later, in a darker room, the left pupil became larger than the right. I did not get the knee or ankle jerks."

Referred to me by Dr. Hyslop in April, 1939, he stated that after repeated assurances from Dr. Hyslop as to the benign nature of his condition he finally put the matter out of his mind. My examination was similar to that made in 1934 except that the right knee jerk was obtained. The left pupil in its resting state was larger than the right.

CASE 5. The 8-year-old son of Case 4. The father noticed that the boy's left pupil was larger than the right when he was 3 years of age. This condition has remained constant since. As the boy was perfectly well in every other respect no medical examination was made until he was brought in to see me at my request in April of this year.

The physical and neurologic examinations were entirely negative except for the anisocoria and diminished ankle jerks—right more than left. The left pupil was larger than the right. Both pupils reacted promptly to light and in accommodation and dilated promptly when the stimulation was removed. Both pupils showed a definite hippus.

While this patient does not show the typical reactions of the Adie pupil, these findings in conjunction with those of the father are highly suggestive. There is one other child in the family—a girl of 11 whose pupillary reactions and deep reflexes are entirely normal.

CASE 6. A 15-year-old Italian girl, showed a dilated left pupil which reacted imperfectly to light and tonically in accommodation. Both ankle jerks were absent and the knee jerks were obtained only on reinforcement. She also had suffered from arrested pulmonary tuberculosis.

This patient was admitted to St. Luke's Clinic (No. 8582) in November,

1937, with pulmonary symptoms dating back to July of that year. A diagnosis of pulmonary tuberculosis was made and an artificial pneumothorax was produced on the left side. She then spent several months in different sanatoria. The inequality of the pupils and absent ankle jerks were first noticed in July, 1938, and she was returned to St. Luke's hospital in August, 1938, for study. Her Wassermann reactions and the blood and spinal fluid were normal. I saw the patient in consultation on September 7, 1938. At that time her left pupil was larger than the right. It reacted poorly and imperfectly to light but was subject to spontaneous variations in size. It showed the typical tonic contraction in accommodation. The knee jerks could only be obtained on reinforcement and the ankle jerks were both absent.

This patient has been seen on repeated occasions since this time, the last visit being in May, 1939. Her pulmonary condition seems to be completely arrested but the pupillary and reflex changes remain the same.

CASE 7 was a 28-year-old single woman of Italian descent showing a dilated left pupil which did not react to light but reacted tonically in accommodation. Both ankle jerks were absent and the knee jerks unequal, the left being greater than the right.

In July, 1938, this patient noticed the difference in the size of her pupils while looking in the mirror. Because of this she reported to the Private Clinic of the Neurological Institute (No. 39090) in August, 1938, and was examined by Dr. Alfred Gallinek who has kindly referred the case to me. At the time of her admission to the clinic in August, 1938, the left pupil was larger than the right. The ankle jerks were absent and the right knee jerk was diminished. The blood Wassermann reaction was negative. The spinal fluid was not examined.

When last seen by me (April, 1939) the pupillary and reflex changes were the same as described by Dr. Gallinek in August, 1938.

**Differential Diagnosis.** The Argyll Robertson pupil is usually bilateral. The pupils are small and irregular. They do not react to light, react promptly in accommodation and dilate promptly once the effort at accommodation ceases. They react imperfectly and slowly to mydriatics. With the exception of the lack of response to light, these characteristics are diametrically opposed to those of the tonic pupil.

Another and to my mind very important characteristic of the Argyll Robertson pupil which differentiates it from other forms has been pointed out by McGrath<sup>30</sup> and that is atrophy of the iris which gives to the syphilitic eye that peculiarity so often noted by older clinicians.

Diphtheria occasionally gives rise to an ophthalmoplegia interna, but never a tonic pupil. The pupillary changes following diphtheria appear about 10 weeks after the onset of the disease, are bilateral and get completely well in a month or two.

True tonic pupils have never been reported as due to epidemic encephalitis\* and no case of Adie's syndrome *per se* has ever shown any of the early or late symptoms of this disease.

The possibility of the tonic phenomenon being related to myo-

\* Jaensch's case showed pallor of the optic discs and enlargement of the blind spots which automatically removes it from the Adie group, as the optic nerve must be intact in the Adie syndrome.

tonia congenita, Thomsen's disease, is one to be reckoned with. However, the absence of myotonic phenomena in skeletal muscles in all of these cases, the fact that repetition does not tend to quicken the reaction of the pupil, and that quinine has no effect upon it, makes this association seem unlikely.

Anisocoria, such as is shown in Case 5, is said to exist frequently in children and in 10% of all normal cases (Fuchs<sup>18</sup>). It may be produced by glaucoma, iritis, refractive errors, or the instillation of some drug. Also it may be observed in intracranial tumors, head injuries, intracranial hemorrhage, meningitis, either central or spinal and those conditions associated with Horner's syndrome. Morax<sup>33</sup> has reported a case of sudden dilatation of one pupil without any other demonstrable ocular or nervous system lesion. Byrne<sup>8</sup> lists the causes of anisocoria as follows: (a) reflex dilatation, (b) inherent dilator tonus, (c) chemical dilator tonus, (d) reflex constriction, (e) inherent constrictor tonus, (f) chemical effector constrictor tonus.

It is plain to be seen that not all cases of anisocoria fall into the group of the Adie syndrome. In the absence of demonstrable ocular and nervous system lesions, especially if there is any familial or hereditary incidence and the inequality of the pupil is associated with diminished or lost ankle jerks, one is justified in placing the case in this group.

The inclusion by Adie of the fixed pupil as an atypical form of this syndrome inasmuch as the fixed pupil is undoubtedly part of many diseases of the nervous system other than the one Adie describes. Within the limits set by Adie in his original description, namely, an unilateral fixed pupil of long standing in a young person, probably a female with or without loss of deep reflexes, but without other neurological signs, this differential diagnosis can and should be made.

**Etiology.** Both the localization of the lesion and the nature of it are still unknown. So far as I know, no autopsy findings on a case of Adie's syndrome have been published. Adie's statement that the tonic pupil is never caused by syphilis has been challenged by the French school and 3 cases of tonic pupil allegedly due to syphilis have been reported by L'hermitte,<sup>29</sup> Harvier<sup>20</sup> and Laignel-Lavastine.<sup>28</sup> In L'hermitte's case the Wassermann reaction was reported as doubtful and in the latter 2 cases the serological reactions were negative. It can be fairly stated that so far syphilis has not been established as the cause of the tonic pupil. Diphtheria and epidemic encephalitis seem definitely to be ruled out.

While this syndrome is associated with other diseases such as epilepsy, arthritis, asthma and pulmonary tuberculosis, in my series, and with influenza, encephalitis, alcoholic polyneuritis, dysthyroid states, various sympathetic disorders, psychopathic states and per-

nicious anemia as cited by Jelliffe<sup>\*25</sup> there is a certain uniform similarity to these cases which I hope that I have illustrated in the accompanying photographs and which is even more forcibly borne in upon one in reviewing the literature. I am therefore inclined to agree with Adie that this is a benign disease *sui generis* and that this syndrome co-exists with the other diseases such as those mentioned above but is not caused by them.

In discussing the etiology from a theoretical standpoint three distinct phenomena must be accounted for. 1, The unilateral dilated pupil which reacts to mydriatics and eserine but not to light. 2, The tonic contraction of the pupil to accommodation—convergence. 3, The absence of ankle jerks and sometimes knee jerks. Under the first category we are obviously dealing with the paralysis of the pupilloconstrictor fibers of the pupil in response to light. These fibers are under the control of the parasympathetic system. The pupillodilator mechanism (sympathetic) is intact. According to Byrne<sup>8</sup> a lesion in the efferent tract is apt to give an unilateral change in the pupil while an afferent lesion is apt to give bilateral changes. Ranson<sup>41</sup> has demonstrated a small tract in the pretectal region between the posterior commissure and the oculomotor nuclei the stimulation of which causes marked constriction of the homolateral pupil and weak dilation of the contralateral pupil. It is conceivable that a paralysis or interruption of this tract would cause the reverse. Phenomenon No. 2 is even more difficult as it requires the existence of a lesion that will alter the tonus of the constrictor muscles of the pupil and ciliary body of one eye only and in a way usually associated with excess secretion of acetylcholine and stimulation of the parasympathetic system which is indeed a paradox. To explain Phenomenon No. 3 one must postulate a lesion which will alter the tonus of the lower extremities in such a way as to abolish the ankle jerk on one or both sides and sometimes the knee jerks. A peculiarly selective lesion in the pretectal region might conceivably account for all of these phenomena but the nature of the lesion is still an enigma.

Dressler<sup>13a,b</sup> reported the existence of this syndrome in 3 sisters of whose family history he made a careful study. Other cases existed in the families of both the mother and the father and there were several members of the family on both sides who exhibited the phenomenon of Hippus either alone or in association with the tonic pupil. On the basis of this family, Dressler believes that Adie's syndrome is an hereditary disease and that the inherited trait is a recessive one.

\* A careful review of the cases referred to by Jelliffe shows them to be a conglomerate group of different types of pupillary disturbances varying from Horner's syndrome to the neurotonic pupil of Westphal. Whereas a tonic pupillary response is described as a transient phase of Wernicke's poliomyelitis superior and other midbrain and hypothalamic lesions, no chronic and enduring pupillary and reflex changes such as Adie describes has ever been shown to result from any of these diseases.

Foster Moore reports a case of a man of 70 who had had a dilated tonic pupil for 40 years, whose sister and grand-daughter were similarly affected. Rudolf<sup>46</sup> reports the existence of this syndrome in mother and daughter. Reese, discussing this paper, referred to a family in which 2 members had Adie's syndrome and other members of the family had Huntington's chorea. In my own series I have examined as many of the relatives of these patients as could be located and except for the father and son reported as Cases 4 and 5, there was no familial or hereditary incidence in this group of cases.

**Incidence.** Aside from Adie's three papers on this subject, published in 1931 and 1932, I have collected 50 additional articles on the subject through the year 1938. The 7 cases in this series have been collected in the last 18 months. This therefore is not a rare disease and I believe it is still frequently overlooked and that many of these cases are still being treated for syphilis in spite of negative serological reactions.

**Summary.** Seven cases of Adie's syndrome are presented and the various theories of the location and nature of the pathology of this condition are discussed. Still lacking definite proof, the facts so far elicited make the following statement tenable. Adie's syndrome is a disease *sui generis*. It runs a chronic and benign course and may exist either alone or in conjunction with other diseases. It is perhaps heredodegenerative in nature, but it is not syphilitic.

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## INTERPRETATION OF THE GLUCOSE TOLERANCE TEST.

### THE NECESSITY OF A STANDARD PREPARATORY DIET.\*

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It has long been known that starvation or restriction of carbohydrate in the diet of animals or man results in a marked decrease in the ability to utilize carbohydrate. Ingestion of a test dose of glucose, under these conditions, produces hyperglycemia, glycosuria and a marked delay in clearing the blood of absorbed glucose. Although most investigators are fully aware of this phenomenon, the knowledge has not been applied in clinical medicine.

The purpose of this report is to emphasize how much the composition of the previous diet may affect the glucose tolerance test and its interpretation. Since, in mild or questionable cases of diabetes mellitus or in the differential diagnosis between non-diabetic and diabetic glycosurias, the glucose tolerance test becomes of major diagnostic importance, one must eliminate any influence which the previous dietary may have had upon the result.

In 1889, Hofmeister<sup>10</sup> found that if he gave a carbohydrate meal to normal dogs that had been starving previously, glycosuria resulted. This phenomenon he called "hunger diabetes." Since that time a number of investigators, working with several species of animals and also with humans, have confirmed and elaborated these findings. Bang,<sup>1</sup> Staub,<sup>14</sup> Goldblatt,<sup>7</sup> du Vigneaud and Karr,<sup>6</sup> and others have all found hyperglycemia, glycosuria and delayed removal of glucose

\* The expense of this study was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.



from the blood stream, when carbohydrate was fed after a period of starvation. Furthermore, it has been shown by Southwood,<sup>13</sup> Greenwald *et al.*,<sup>8</sup> Sweeney,<sup>15</sup> Malmros,<sup>11</sup> and Tolstoi<sup>17</sup> that diets low in carbohydrate lead to the same type of response following ingestion of a test carbohydrate meal.

Dann and Chambers<sup>4a</sup> observed that a few days of carbohydrate feeding were sufficient to restore to normal the decreased utilization of carbohydrate induced by prolonged starvation. Sweeney<sup>16</sup> demonstrated that a single preliminary dose of glucose did not succeed in counteracting the effects of an abnormal antecedent diet.

A discussion of the mechanisms by which carbohydrate tolerance is lowered during starvation or under conditions of low carbohydrate intake is beyond the purpose of this paper. Much excellent work, however, dealing with this question, has been reported by Dann and Chambers<sup>3,4b,c</sup> and more recently by Haist, Ridout and Best.<sup>9</sup> Suffice it to say that this factor as a depressing influence upon carbohydrate utilization can be completely eliminated by a relatively short period of high carbohydrate feeding.

We have encountered a sufficient number of patients (referred to our clinic for treatment of diabetes mellitus) whose diminished tolerance for carbohydrate was based upon a deficient intake of carbohydrate, to make us realize the importance of this factor in clinical medicine.

**Experimental Procedures.** Early in this work we observed that the presence of undernutrition *per se* was important in determining the degree to which carbohydrate tolerance would be diminished by restriction of carbohydrate in the diet. We, therefore, chose as subjects for study 3 malnourished but otherwise normal patients, 3 normally nourished men (medical students) and 3 normally nourished women (dietitians). All 9 subjects were between the ages of 19 and 25. All were fed a standard preparatory diet (300 gm. CHO, 80 gm. P and 3000 cal.) for 3 days before the initial glucose tolerance test was done.\* All gave the normal response. They were then fed a diet containing 20 gm. of carbohydrate, 50 gm. of protein and 1600 calories for 5 days following which the glucose tolerance test was repeated. Thus, the effect upon normal carbohydrate tolerance of a short period of sharp carbohydrate restriction was observed.

In addition, data are included on 3 patients wrongly diagnosed as diabetics. In these, the effect upon diminished carbohydrate tolerance of a short period of normal carbohydrate intake was observed.

**Results.** Table 1 shows the effects of different diets for short periods of time upon carbohydrate tolerance in normal and undernourished young men and women. A remarkable delay in clearing

\* Glucose (1.75 gm. per kg. of body weight) given orally in the postabsorptive state was used as the test dose. Blood sugar was done by the Benedict method.<sup>2</sup>

the blood of absorbed glucose is produced in normally nourished people by a 5-day period of dietary restriction. Qualitatively the response is the same in the undernourished individuals. The degree of response to the same restriction, however, is much greater in the undernourished group. Since, initially, both groups responded to 3 days of normal dietary by giving a normal glucose tolerance curve, it must be concluded that the existence of undernutrition makes the individual more susceptible to short periods of carbohydrate restriction. Chart 1 shows the composite response of each group to high and low carbohydrate preparation.\*

TABLE 1.—EFFECT OF ANTECEDENT DIETARY CARBOHYDRATE UPON GLUCOSE TOLERANCE TEST.

Normal Young Men and Women.														
					Previous diet—3 days: 300 CHO, 80 P, 3000 cals.					Previous diet—5 days: 20 CHO, 50 P, 1600 cals.				
					Blood sugar, mg. per 100 cc.					Blood sugar, mg. per 100 cc.				
Sex.	Age.	Ht., in.	Wt., lbs.	Under- weight, %.	F.	1 hr.	2 hr.	3 hr.	4 hr.	F.	1 hr.	2 hr.	3 hr.	4 hr.
M	24	70	151	2	77	65	74	58	58	58	195	116	93	61
M	24	69	163	0	78	81	62	58	58	68	202	124	65	64
M	25	68	152	0	77	67	75	44	68	73	198	105	40	75
F	24	63	121	0	82	91	70	80	72	69	178	137	111	61
F	21	61	121	0	71	83	71	67	70	57	154	174	91	54
F	23	68	147	0	80	138	80	56	62	65	221	149	129	48
Average:					77	84	74	60	67	65	191	134	88	61

Undernourished Young Men and Women.														
M	25	72	142	16	64	122	105	45	48	44	214	242	126	76
M	25	72	138	17	78	182	115	44	..	67	250	188	53	..
F	19	62	103	14	75	96	72	60	68	64	244	250	182	89
Average:					72	133	97	50	58	58	236	227	120	83

The additional 3 cases which we have chosen as examples indicate how an erroneous diagnosis of diabetes mellitus can be made, when the important factor of previous carbohydrate restriction is neglected. The first patient had been diagnosed and treated for diabetes with diet and insulin before coming to the University Hospital. The second had been considered to have mild diabetes and the third was said to have had diabetes for 20 years.†

**Case Reports.** CASE 1.—M. R., 5 feet 4 inches tall, a 21-year-old, white, married woman, was admitted to the University Hospital on Jan. 10, 1937, with a chief complaint of severe headaches. Marital difficulties accounted for an anxiety state. She had lost all desire for food and the weight had fallen from 115 to 94 pounds in 6 months. One month before admission glycosuria was found while she was under treatment in another hospital. A diet restricted in carbohydrate was given and 2 doses of insulin injected daily.

On admission to this hospital glycosuria was found again. Except for malnutrition the physical examination showed no abnormalities. A glucose tolerance test was done without consideration of the previous diet. The result was as follows: Fasting 83 mg. per 100 cc.; 1 hour, 238; 2 hours, 198;

\* It seems worth remarking that carbohydrate restriction produced in the females of both groups a greater loss of carbohydrate tolerance than it did in the males.

† Case histories have been condensed to conserve space.

3 hours, 182. Sugar was found in all specimens of urine after ingestion of the glucose. The patient was then referred to the diabetic clinic for treatment.

In order to rule out the factor of previous carbohydrate restriction we fed her the standard preparatory diet for a period of 2 weeks during which time she gained 3 pounds in weight. The glucose tolerance test was repeated and resulted in a normal response (Chart 2). A low carbohydrate diet (20 gm. CHO, 50 gm. P, 1600 cal.) was then given for 7 days. She lost 4 pounds. It is seen from the chart that the curve rose even higher than that obtained on admission. Again the normal diet for 7 days associated with a gain of 5 pounds brought the response to normal.

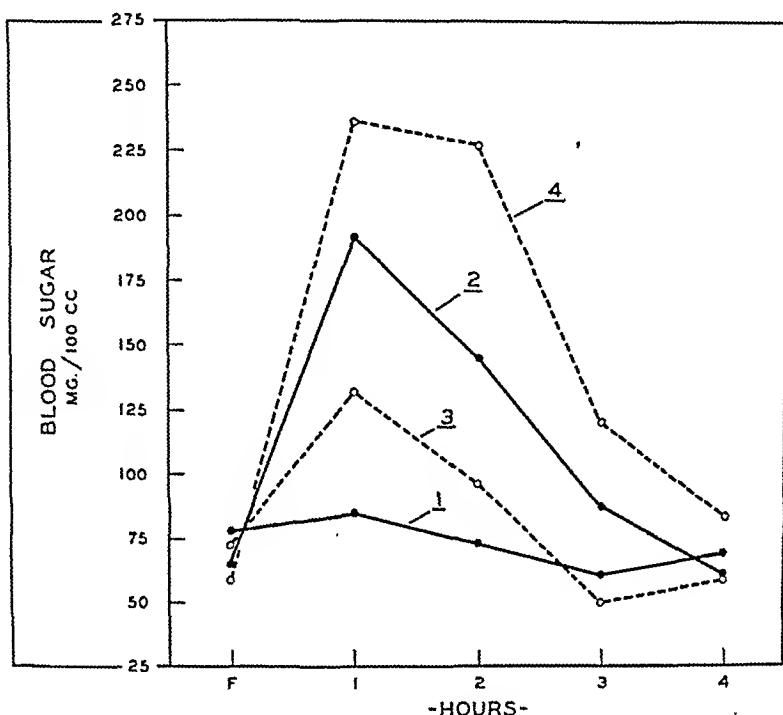


CHART 1.—Effect of previous diet upon glucose tolerance of normal and undernourished individuals.

- |  |                                  |
|--|----------------------------------|
| 1.—Normals—after 3 days of 3000 cal. 300 gm. CHO, 80 gm. P.        | } Composite curves of 6 subjects |
| 2.—Normals—after 5 days of 1600 cal. 20 gm. CHO, 50 gm. P.         |                                  |
| 3.—Undernourished—after 3 days of 3000 cal. 300 gm. CHO, 80 gm. P. | } Composite curves of 3 subjects |
| 4.—Undernourished—after 5 days of 1600 cal. 20 gm. CHO, 50 gm. P.  |                                  |

*Comment.* This case serves to emphasize how promptly and with what magnitude glucose tolerance will be affected by changes in the preparatory dietary carbohydrate in a malnourished but otherwise normal individual.

CASE 2.—A. W., male, aged 72, 5 feet 5 inches tall, weight 108 pounds, entered the University Hospital on April 13, 1938, because of bladder

calculi. A heavy glycosuria was found on routine urine examination. In the preceding 3 weeks he had lost his appetite and 6 pounds in weight. A glucose tolerance test, done without consideration of the previous dietary, was found to be: Fasting, 85 mg. per 100 cc.; 1 hour, 224; 2 hours, 212; 3 hours, 138. Glycosuria appeared in all of the urine specimens collected after the glucose ingestion. He was referred to the diabetic clinic for treatment.

He was given the standard normal diet for 8 days during which he gained 4 pounds in weight. Chart 3 shows the glucose tolerance responses after 5 days of this diet and again after 8 days.

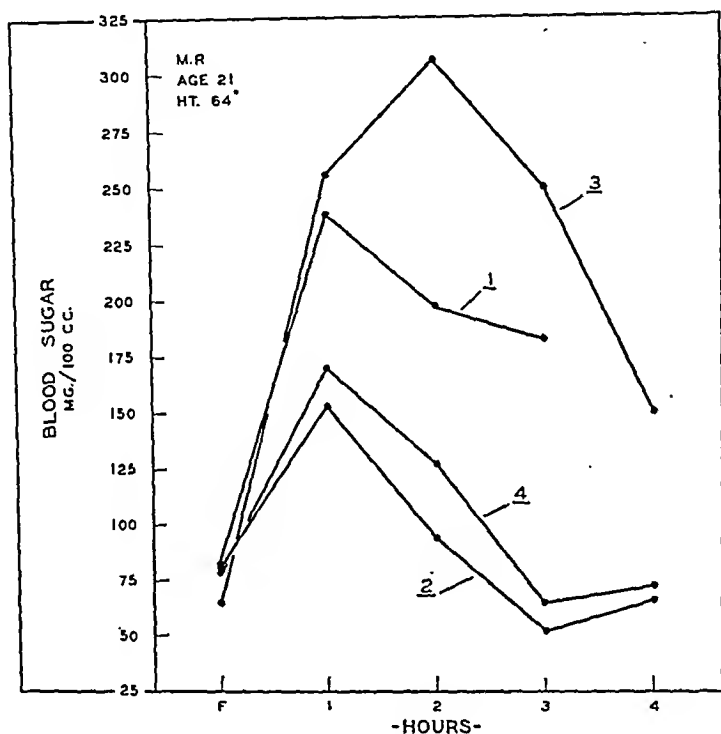


CHART 2.—Case 1.

- |                             |                        |                |
|-----------------------------|------------------------|----------------|
| 1. Test done on admission.  |                        | Weight 94 lbs. |
| 2. After 2 weeks 3000 cals. | 300 gm. CHO, 80 gm. P. | Weight 97 lbs. |
| 3. After 7 days 1600 cals.  | 20 gm. CHO, 50 gm. P.  | Weight 93 lbs. |
| 4. After 7 days 3000 cals.  | 300 gm. CHO, 80 gm. P. | Weight 98 lbs. |

*Comment.* Two points are worthy of mention: (1) That following long-standing undernutrition and carbohydrate restriction, it may require more than 5 days of high carbohydrate feeding to effect complete return of normal carbohydrate tolerance. (2) The final curve, which we consider normal, reaches a peak of 184 mg. per 100 cc. in the first hour. This is higher than any of the curves on the other subjects following the preparatory diet. It has been shown, however, that normal old people exhibit a somewhat lower tolerance for carbohydrate than young people.<sup>5,12</sup> This probably accounts for the difference.

CASE 3.—A. O., male, aged 62, 5 feet 6 inches tall, weight 149 pounds, was first admitted to the University Hospital on Dec. 11, 1934, with a typical story of peptic ulcer. A heavy glycosuria was found in the routine urine examination. He said that he had been considered a diabetic for 20 years because sugar had been found consistently in his urine during that time. On several occasions he had been treated by mild restriction of dietary carbohydrate without affecting the glycosuria. On admission (1934) he was given a low carbohydrate diet. The glycosuria promptly cleared. After having been on this diet (20 CHO, 50 P, 1600 cal.) for 4 days a glucose tolerance test was done in order that the diagnosis be confirmed. No thought, however, was given to the fact that he had been

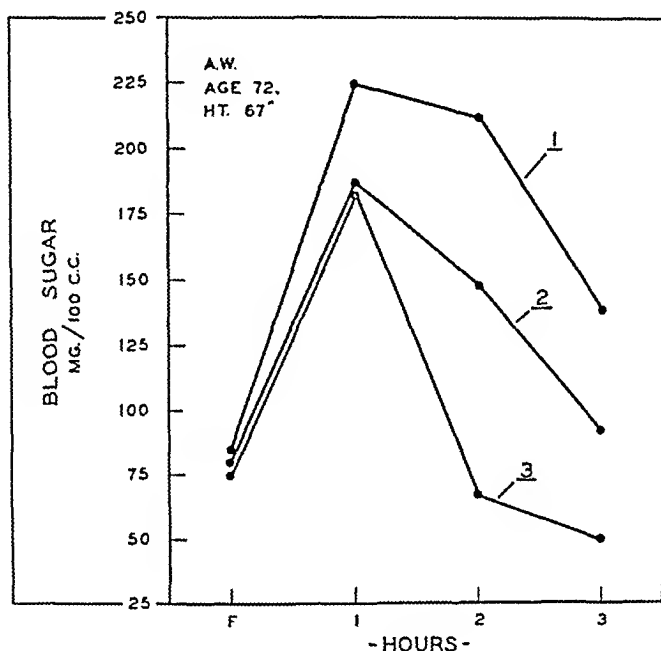


CHART 3.—Case 2.

- |  |                 |
|--|-----------------|
| 1. Test done on admission.                       | Weight 108 lbs. |
| 2. After 5 days 3000 cal. 300 gm. CHO, 80 gm. P. | Weight 112 lbs. |
| 3. After 8 days 3000 cal. 300 gm. CHO, 80 gm. P. | Weight 113 lbs. |

prepared for the test on a low carbohydrate diet. The result was as follows: Fasting, 65 mg. per 100 cc.; 1 hour, 223; 2 hours, 218; 3 hours, 124. Glycosuria occurred in all specimens after glucose ingestion. This was considered to indicate impaired utilization of carbohydrate. The carbohydrate of the diet was gradually raised and it was found that 150 gm. of carbohydrate daily was all that could be tolerated without glycosuria. He was, therefore, discharged as a diabetic on Dec. 29, 1934, with a diet containing 150 gm. of carbohydrate and maintenance calories. He remained on this diet for over 3 years and returned on Mar. 14, 1938, for a reexamination of his diabetic status. There had, in the interim, been intermittent glycosuria.

His weight on Mar. 14, 1938, was 148 pounds (149 on the original admission). He was given 3000 calories, 300 gm. of carbohydrate and 80 gm. of protein daily for 6 days during which time glycosuria was almost always

present. A glucose tolerance test at the conclusion of this preparatory period showed a normal curve (Chart 4) but the urine specimens during the test indicated that the renal threshold for glucose was somewhere between 90 and 112 mg. per 100 cc. He was discharged on an unrestricted diet and told that he had renal glycosuria.

*Comment.* This case indicates how a patient with renal glycosuria can be misdiagnosed as a diabetic when the glucose tolerance test is done after a period of carbohydrate restriction. Continuous glycosuria, because of a low renal threshold, resulted in the pre-

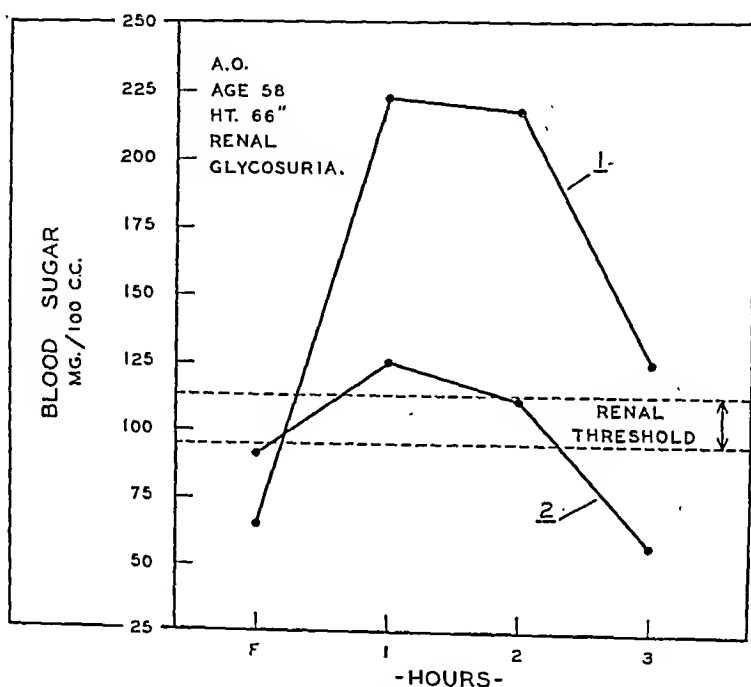


CHART 4.—Case 3.

1. After 4 days 1600 cal. 20 gm. CHO, 50 gm. P (1934). Weight 149 lbs.
2. After 5 days 2000 cal. 300 gm. CHO, 80 gm. P (1938). Weight 148 lbs.

scription of a diet limited in carbohydrate. A glucose tolerance test, under these conditions, revealed a diabetic type of response. Thus, the usual criteria for the diagnosis of diabetes mellitus were satisfied. A glucose tolerance test after adequate carbohydrate preparation, however, disclosed normal carbohydrate tolerance and renal glycosuria. In this case malnutrition was not a factor. The original abnormal response was the result of previous carbohydrate restriction.

*Discussion.* It has been shown repeatedly that restriction of dietary carbohydrate in the normal individual results in a significant decrease in the rate of utilization of glucose. Yet it is not customary to scrutinize the antecedent dietary of the patient before interpreting the glucose tolerance test. The experiments reported here

show again how greatly the normal rate of glucose utilization can be depressed by sharply limiting the intake of carbohydrate for several days prior to the test. In addition, it is found that when undernourished individuals, exhibiting normal carbohydrate tolerance, are subjected to the same restriction, a more marked delay in the utilization of glucose results. Examples of erroneous diagnoses of diabetes, due to failure to recognize previous restriction of dietary carbohydrate, are cited.

Claims have been made that the glucose tolerance test is a poor indicator of the ability of the organism to dispose of carbohydrate. We believe that much of the confusion arises from the lack of standardized preparatory period prior to the performance of the actual test. Much has been done to standardize the technique of doing the test, such as dosage of glucose per unit of body weight, time of obtaining blood samples, and so on. But in clinical practice, at least, the important influence of the previous dietary has been neglected. In order to obtain more standardized and comparable glucose tolerance tests we have modified the procedure by insisting that a standard preparatory diet be eaten for at least 3 days before the test is done. This diet is made up of 300 gm. of carbohydrate, 80 gm. of protein and, at least, maintenance calories. In cases in which it is known beyond question that the dietary of the preceding few days has been adequate for maintenance and abundant in carbohydrate one need not prepare the patient. When one encounters a diabetic type of glucose tolerance test with a fasting blood sugar value at or near normal, he should repeat the test after adequate dietary preparation. The objection that such a procedure entails greater effort and time does not justify errors in diagnosis due to lack of such procedure.

Diabetics who have taken the standard preparatory diet for three to five days have not been harmed in any way. The temporary increase in glycosuria disappears shortly after the test diet is discontinued.

In most cases, however, a glucose tolerance test is not necessary in order to make the diagnosis of diabetes. It is in the mild cases or in ruling out non-diabetic glycosurias that the glucose tolerance test becomes of major diagnostic importance. These are just the cases in which an erroneous diagnosis of diabetes may be made if, previous to the test, the intake of food has been limited.

The same preparatory precautions must be applied in any condition in which the glucose tolerance curve is to be used as a help in diagnosis. In hyperinsulinism, for example, the glucose tolerance curve often shows a precipitous fall to hypoglycemic levels when done after the standard preparatory diet. Restriction of dietary carbohydrate for several days before the test results in a much less marked drop of the blood sugar. Hence, under these conditions, the glucose tolerance test loses its value as a diagnostic aid.

Thus it appears evident that in order that glucose tolerance tests be in any way comparable and worthy of interpretation, they must be preceded for several days by the ingestion of an adequate diet. Our standard preparatory diet list is seen in Table 2.

TABLE 2.—STANDARD PREPARATORY DIET.  
(80 gm. protein, 300 gm. carbohydrate, 2800 cal.)

*Diet Plan.*

*Breakfast:*

Fruit . . . . .	1 serving
Cereal . . . . .	1 serving
Bread . . . . .	2 slices
Butter . . . . .	1 tablespoon
Cream . . . . .	$\frac{1}{2}$ cup
Jelly or sugar . . . . .	2 tablespoons
Beverage	

*Dinner:*

Meat or substitute . . . . .	1 large serving
Potato or substitute . . . . .	1 serving
Cooked vegetable or	
Salad . . . . .	1 serving
Bread . . . . .	1 slice
Dessert	
Jelly or sugar . . . . .	2 tablespoons
Butter . . . . .	2 tablespoons
Cream . . . . .	3 tablespoons
Beverage	

*Supper:*

Meat or substitute . . . . .	1 medium serving
Potato or substitute . . . . .	1 serving
Cooked vegetable or	
Salad . . . . .	1 serving
Bread . . . . .	2 slices
Dessert	
Jelly or sugar . . . . .	2 tablespoons
Butter . . . . .	2 tablespoons
Beverage	

One pint of milk daily is added to the above diet plan. Coffee and tea may be taken as desired. One ounce of sugar candy may be substituted for 2 tablespoons of sugar or jelly.

**Conclusions.** 1. A short period of carbohydrate restriction in the normal person causes a marked delay in the rate of utilization of carbohydrate as indicated by the glucose tolerance test.

2. Undernourished individuals respond to the same procedure with a greater loss of carbohydrate tolerance.



3. Erroneous diagnoses of diabetes mellitus are made when the factor of previous carbohydrate restriction is neglected.

4. Unless the influence of previous carbohydrate restriction is removed by means of an adequate preparatory diet, the glucose tolerance test is not reliable as an indicator of the individual's ability to utilize carbohydrate.

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### THE COMPOSITION OF INTRAPLEURAL AIR IN ARTIFICIAL PNEUMOTHORAX.

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NEARLY 150 years ago Astley Cooper (quoted by Abernethy<sup>1</sup>) injected air into the pleural cavity and demonstrated that it caused no inflammation. Between 1888-1892 Forlanini (according to Hamman and Sloan<sup>6</sup>) instituted injection of gas into one pleural cavity as a therapeutic measure in the treatment of pulmonary tuberculosis. Interest in the composition of gas present in the pleural cavity began with John Davy.<sup>5</sup> His analyses did not give accurate results because they were made postmortem, when the carbon dioxide tension is greatly increased and the oxygen tension decreased. Since then many workers have been interested in this problem (see Campbell<sup>2</sup>). In 1932, Coryllos<sup>4</sup> published a preliminary report of analyses of the intrapleural air in patients with artificial pneumothorax.

In a healthy pleural cavity, no matter what the composition of the gas injected may be, the mixture resulting after equilibrium has been established (*i. e.*, after about 2 days) has the same composition,

namely, oxygen 2 to 4% and carbon dioxide 6 to 8%. In the case of artificial pneumothorax in pulmonary tuberculosis this composition is modified by variations in the degree of collapse, histologic changes in the pleura, the presence of fluid or inflammatory processes and the presence of broncho-pleural fistulæ.

The present study was undertaken in an attempt to confirm Coryllos' findings and, if possible, to apply them in the practical management of artificial pneumothorax.

After a preliminary pressure reading, a sample of intrapleural air was withdrawn into an oiled syringe, and a sample of fluid, if any was present, was obtained for bacteriologic study. Serial analyses were performed on selected cases and, whenever possible, findings were checked postmortem. Seventy-four analyses were done on 35 patients. An attempt was made to classify the results according to the type of fluid (if any) present, as Coryllos had done.\* While a rough correlation was obtained, it was found that the composition of the intrapleural air, especially in cases of long-standing pneumothorax, was so modified by other factors as to limit the usefulness of such a classification. The oxygen values in particular were difficult to interpret in terms of any single factor. They showed a tendency to vary inversely with the carbon dioxide values, but there were numerous exceptions. Our failure to confirm the findings of Coryllos with respect to the sharp demarcation of his groups may have been due partly to difference in the type of patient studied. The majority of the cases which we studied were characterized by pneumothorax of long standing with either chronic or intermittent fluid. It is possible that vascular and histologic changes in the pleura may have been important modifying factors with regard to the composition of the intrapleural air.

Since the diffusibility of carbon dioxide through living membranes is 20 to 30 times as great as that of oxygen, it would, *a priori*, be expected that oxygen might fail to reach equilibrium with the surrounding tissues in those cases in which pleural permeability has been reduced by inflammatory processes. Accordingly, we have classified our results according to the percentage of carbon dioxide in the intrapleural air. In Group I, the intrapleural air contained more than 10% carbon dioxide; Group II, 8 to 10%; Group III, 6 to 8%; and Group IV, less than 6%.

GROUP I (28 analyses on 16 patients). Of the 16 patients in this group, all had fluid which contained tubercle bacilli. One patient had a clear fluid, 11 had frankly purulent fluid, while the other 4 had fluid which was intermittently purulent. It is significant that the composition of the intrapleural air in the cases of intermittent

\* Coryllos<sup>3</sup> gave the following classification:

- (a) No fluid.  $\text{CO}_2 = 6\%$ .  $\text{O}_2 = 3$  to  $4\%$ .
- (b) Straw-colored fluid.  $\text{CO}_2 = 6$  to  $8\%$ .  $\text{O}_2 = 1$  to  $2\%$ .
- (c) Purulent fluid.  $\text{CO}_2 = \text{more than } 8\%$ .  $\text{O}_2 = \text{less than } 1\%$ .

fluid often remained practically unchanged for weeks following complete reabsorption of the fluid, so that the presence or absence of fluid and the type of fluid cannot be the sole determining factors. For this reason, single analyses are often of little value; whenever possible serial analyses should be performed. Only in this way can the presence of small broncho-pleural fistulæ, which are intermittently sealed off by the fluid, be revealed. As an example, the case of S. G. may be considered:

CASE 1.—S. G., a 41-year-old Negress with tuberculosis of the lymph nodes and a far advanced, exudative tuberculous process involving areas throughout the right lung and the upper half of the left lung, had a right artificial pneumothorax instituted August 2, 1938. On September 21, 1938, the patient developed an acute pleurisy with effusion on the right side, and has continued to form fluid to date (June 1, 1939). Pressure readings are obtained with difficulty, but have never been suggestive of a broncho-pleural fistula. The patient has never raised pleural fluid with sputum. General condition at present (June 1, 1939) is poor.

*Intrapleural air analyses.* 11-9-38  $\text{CO}_2 = 10.23$ ,  $\text{O}_2 = 3.53$ . 450 cc. clear, dark fluid, positive for tubercle bacilli on concentrate smear.

11-23-38  $\text{CO}_2 = 10.12$ ,  $\text{O}_2 = 4.34$ . 300 cc. fluid, as above.

12-7-38  $\text{CO}_2 = 8.46$ ,  $\text{O}_2 = 5.88$ . 300 cc. fluid, as above.

2-10-39  $\text{CO}_2 = 6.92$ ,  $\text{O}_2 = 7.92$ . 300 cc. clear fluid, neg. T.B. on smear, pos. on culture. Analyses show trend toward fistula, but no clinical signs.

2-27-39  $\text{CO}_2 = 2.94$ ,  $\text{O}_2 = 15.10$ . Some fluid present, not aspirated. Analyses and clinical signs are now definitely indicative of fistula. Intrapleural pressures atmospheric.

5-29-39  $\text{CO}_2 = 10.47$ ,  $\text{O}_2 = 0.22$ . Fluid now purulent. Fistula has closed.

The oxygen values of the intrapleural air in Group I patients varied from 0.22 to 4.59%. The higher values were obtained in cases of intermittent fluid and of small broncho-pleural fistulæ periodically sealed off by fluid. In view of the much greater disparity between the oxygen concentration of intrapleural and alveolar air as compared with the corresponding values for carbon dioxide, and since, furthermore, oxygen is much less diffusible than carbon dioxide, it might be expected that oxygen values would vary more widely than carbon dioxide values in cases of this type. For this reason, carbon dioxide concentration is of greater significance in following the course of fluid formation and reabsorption, while the oxygen values in serial analyses reveal the presence of fistulæ intermittently closed, as well as giving some indication of the degree of impairment of permeability in thickened pleuræ.

GROUP II (10 analyses on 8 patients). All the patients in this group had fluid in the pleural cavity. Only one of these fluids was purulent, while the others were all recent effusions. It is a remarkable fact that in 5 out of the 7 cases of recent acute effusions, the oxygen concentration of the intrapleural air was 1% or less, a value which Coryllos found only in cases of purulent fluid. After

the fluid had been present for a variable length of time (1 week up to several months), the oxygen concentration rose to 2 to 3%, the value which we have found to be characteristic of clear fluids. The oxygen concentration of intrapleural air is presumably determined by two factors: the utilization of oxygen by the leukocytes and organisms present in the pleural fluid, and secondly, by the type of equilibrium established between the intrapleural air and the surrounding tissues and fluids. The latter factor has been discussed at some length by Matsuzawa<sup>7</sup> and Campbell.<sup>2</sup> Neither of these workers is able to explain the low oxygen concentration of intrapleural air after stabilization of a pneumothorax. Apparently, in the cases of recent acute effusions presented above, equilibrium between intrapleural air and the surrounding tissues and fluids was not attained until the acute symptoms attending the formation of the effusion had subsided. This is another example of the danger of depending on single analyses, particularly with reference to oxygen values, in the interpretation of fluid formation and reabsorption. Further emphasis is given to this point by the fact that the highest intrapleural oxygen value in this entire group occurred in the only case in which the pleural fluid was purulent.

GROUP III (10 analyses on 7 patients). Of the 7 patients in this group, 3 had no fluid, 3 had clear fluid, and 1 had no fluid at the time of the first analysis but developed fluid during the period in which serial analyses were performed. The average values were as follows:

- (a) No fluid       $-\text{CO}_2 = 6.68, \text{O}_2 = 3.31.$
- (b) Clear fluid     $-\text{CO}_2 = 7.52, \text{O}_2 = 2.61.$
- (c) Fluid forming—(1) no fluid.  $\text{CO}_2 = 6.88, \text{O}_2 = 4.67.$   
                          (2) clear fluid present.  $\text{CO}_2 = 9.52, \text{O}_2 = 1.08.$

GROUP IV (16 analyses on 10 patients). This group is of interest in connection with the diagnosis of broncho-pleural fistula. The average  $\text{CO}_2$  value was 3.63% (range 0.49 to 5.49%). The average  $\text{O}_2$  value was 12.39% (range 4.74 to 19.63%). Five of the 10 patients in this group had clinical symptoms of fistulae, confirmed postmortem in 2 cases. The case of O. Y. is typical.

CASE 2.—O. Y., a 41-year-old white male of Slavic descent, entered Herman Kiefer Hospital on May 25, 1936, with far advanced bilateral tuberculosis. Left artificial pneumothorax was unsuccessful, but right pneumothorax was established on June 1, 1936. Purulent fluid subsequently developed in this space and was aspirated frequently until it disappeared in November, 1937. The space remained free of fluid until May 18, 1938, when a spontaneous collapse of the right lung occurred, with initial intrapleural pressure reading of +6, +11. Purulent fluid then reappeared and persisted until death on March 2, 1939. The following statement is quoted from the autopsy report:

"The right lung is completely collapsed against the medial wall. The pleural surfaces are covered with a thin, purulent exudate, smears of which

reveal acid-fast bacilli and staphylococcus albus. Below the middle of the anterior margin of the upper lobe is a deep indentation, in the base of which there is a rounded opening from which air escapes on inflation of the lung through the trachea."

*Intrapleural air analyses.* 6-6-38  $\text{CO}_2 = 13.53$ ,  $\text{O}_2 = 6.03$ . Small amount of thick, purulent fluid. Spontaneous pneumothorax May 18, 1938. Intrapleural pressures highly positive.

7-27-38  $\text{CO}_2 = 1.70$ ,  $\text{O}_2 = 19.40$ . 400 cc. thick purulent fluid. Pressures highly positive.

8-3-38  $\text{CO}_2 = 1.68$ ,  $\text{O}_2 = 19.60$ . 300 cc. thick, purulent fluid. Pressures remained unchanged before and after removal of 300 cc. fluid, saline irrigation and injection of 20 cc. of gomenol.

8-10-38  $\text{CO}_2 = 1.21$ ,  $\text{O}_2 = 19.97$ . 600 cc. thick, purulent fluid.

8-24-38  $\text{CO}_2 = 1.34$ ,  $\text{O}_2 = 19.45$ . 300 cc. thick, purulent fluid. Open drainage established August 31, 1938. Patient died March 2, 1939.

The other 5 cases had very similar analyses without clinical signs of fistulae. Coryllos<sup>3</sup> reported similar cases in which fistulae were found postmortem. Apparently, then, intrapleural air analyses are more reliable than are clinical symptoms in diagnosing broncho-pleural fistulae.

**Discussion.** The present work confirms the findings of Coryllos, without reservation, *only* with regard to the diagnosis of broncho-pleural fistulae. Even here, unless the fistula is quite large, it is likely to be intermittently closed by fluid, obscuring the changes in intrapleural air and necessitating serial analyses.

In the absence of a fistula, the  $\text{CO}_2$  percentage of the intrapleural air is a fairly reliable index of the type of fluid present, at least during the period of formation. The case of I. S. illustrates this point:

**CASE 3.**—I. S., a 14-year-old Negress, had bilateral pulmonary tuberculosis and severe, but easily regulated, diabetes. Intrapleural air analyses and intrapleural pressure suggested presence of broncho-pleural fistula, and for this reason, a right phrenic crush was performed on November 18, 1938. Fistula closed and 48 hours later fluid appeared for the first time and persisted until death, which occurred January 31, 1939. Postmortem examination revealed collapse of right lung and thick, purulent empyema fluid in right pleural space.

*Intrapleural air analyses.* 11-11-38  $\text{CO}_2 = 4.58$ ,  $\text{O}_2 = 13.30$ . Spontaneous pneumothorax on October 26, 1938. No clinical signs of fistula. No fluid present.

11-16-38  $\text{CO}_2 = 6.50$ ,  $\text{O}_2 = 5.17$ . Has clinical signs of fistula. No fluid but costal angle blurred.

11-21-38  $\text{CO}_2 = 8.57$ ,  $\text{O}_2 = 2.68$ . 300 cc. clear fluid, positive tubercle bacilli on culture. Fluid appeared November 20, 1938, following phrenic crush on November 18, 1938, which closed the fistula.

12-7-38  $\text{CO}_2 = 11.18$ ,  $\text{O}_2 = 4.22$ . 300 cc. clear fluid, which turned purulent a few days later. Patient died January 31, 1939.

When fluid is being periodically formed and reabsorbed, intrapleural air analyses may be misleading. Fluid may entirely disappear without causing an appreciable change in the composition of the air present. This is possibly to be explained by the great

thickening of the pleura often found in these patients, which results in marked decrease in permeability to gases. Residual amounts of fluid rich in leukocytes and organisms may be a contributing factor. The case of B. P. is typical:

CASE 4.—B. P., a 34-year-old Italian male, had far advanced pulmonary tuberculosis involving the upper two-thirds of each lung. Following right pneumothorax he developed fluid in the right pleural space. This fluid cleared and reappeared on several occasions. General condition has shown marked improvement.

*Intrapleural air analyses.* 10-26-38  $\text{CO}_2 = 11.64$ ,  $\text{O}_2 = 2.03$ . 300 cc. cloudy fluid, positive tubercle bacilli on culture.

2-24-39  $\text{CO}_2 = 12.13$ ,  $\text{O}_2 = 0.75$ . Fluid reabsorbing.

2-27-39  $\text{CO}_2 = 11.95$ ,  $\text{O}_2 = 0.96$ . No fluid present.

5-19-39  $\text{CO}_2 = 11.74$ ,  $\text{O}_2 = 1.97$ . 175 cc. clear fluid present.

The oxygen values of the intrapleural air are difficult to interpret. After stabilization of a pneumothorax, and in the absence of fluid, the oxygen tension is lower than that of any of the surrounding tissues and fluids, as was pointed out by Matsuzawa.<sup>7</sup> With the onset of fluid, especially if attended by acute symptoms, the oxygen tension may drop sharply, only to rise again after subsidence of the symptoms. With this exception, there seems to be a rough inverse relation between oxygen tension of the intrapleural air and purulency of the fluid. Oxygen analyses are of greatest value in following the course of broncho-pleural fistulæ, intermittently closed by fluid, because of the slow rate of reabsorption of oxygen. The reason for the initial drop in oxygen tension in cases of hot effusions is unknown.

**Summary and Conclusions.** An attempt has been made to confirm the findings of Coryllos, who reported a high degree of correlation between the composition of intrapleural air and the type of fluid, if any, present in the pleural cavity. The validity of the diagnosis of broncho-pleural fistulæ by means of intrapleural air analyses has been confirmed. In the absence of fistulæ, a fair degree of correlation has been found between the carbon dioxide tension of intrapleural air and the purulency of the fluid, except in cases of intermittent formation and reabsorption of fluid. The oxygen analyses have been found useful in the study of small fistulæ periodically closed by fluid, but the degree of correlation between oxygen tension of intrapleural air and purulency of fluid was rather low. In many cases single analyses of intrapleural air are likely to be misleading; serial analyses should always be performed when possible.

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## BOOK REVIEWS AND NOTICES

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THE NEUROGENIC BLADDER. By FREDERICK C. McLELLAN, M.S., M.D., Instructor in Surgery, University of Michigan Medical School, Ann Arbor. Pp. 206; 9 illustrations and 49 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, \$4.00.

IN view of the confusion in the minds of practitioners, surgeons and neurologists on the diagnosis and treatment of the neurogenic bladder, it is surprising that a monograph such as the author's was not written long ago. The author deserves praise for his efforts in gathering together the abundant though scattered literature on the subject and is to be congratulated on his success in welding it into a coherent presentation of the subject. To this task he brings his personal experience derived from the cystometric study of 500 cases.

The first half of the monograph is devoted to the nervous anatomy and physiology of the bladder and to its anatomic and physiologic relationships to the spinal and suprasegmental levels of the nervous system. Because of its theoretical interest and diagnostic implications this section will be especially attractive to neurologists and neurosurgeons. The second part of the book is given over to the clinical classification and description of the various types of bladder dysfunctions and their diagnosis by cystometry, a detailed description of the cystometric technique and a discussion of the differential diagnosis between the neurogenic bladder and the various kinds of local bladder disease. There is a short but adequate section on the treatment of the neurogenic bladder. An appendix of 49 cystometric charts is included to illustrate the text.

The monograph suffers from some faults in organization. The cystometric charts would be more valuable if they accompanied the text rather than being placed in an appendix. There is considerable reduplication of material and repetition of ideas. The style while simple at times lacks clarity in several sections, particularly those dealing with spinal and cerebral neurophysiology. The author's nihilistic attitude toward the value of the parasympathetico-mimetic drugs in treatment conflicts with current trends and the claims advanced for their efficacy. He is also pessimistic concerning the value of presacral neurectomy. In view of his large experience the author's arguments against these procedures are convincing. In spite of the prevalence of the term "neurogenic," we must protest against a barbarism which is in the same class as "the acute abdomen" and the "operated patient." Why not the equally brief and more correct term, "neuropathic bladder"?

Comforting to many readers will be his championship of the indwelling catheter in the treatment of bladder paralysis consequent to sacral cord lesions. The recent but rather general aversion to the use of this venerable instrument seems to be unfounded especially if proper precautions are taken to prevent peri-urethral infections.

The new methods of providing tidal flow are said to have certain advantages in the control of infection but the author doubts their value as a re-educator of bladder function, a claim that has been made by the inventors of the device.

A complete bibliography particularly of the English literature adds to the value of this timely and excellent monograph.

I. R.

EXPERIMENTAL PHARMACOLOGY AND MATERIA MEDICA. By DENNIS E. JACKSON, PH.D., M.D., F.I.C.A., Professor of Pharmacology, Materia Medica, and Therapeutics in the University of Cincinnati, College of Medicine, etc. Pp. 906; 892 illustrations, including 55 color plates. Second edition. St. Louis: The C. V. Mosby Company, 1939. Price, \$10.00.

THIS will be a valuable reference book for both students and instructors of pharmacology and physiology insofar as it represents an unusually complete collection of the various methods (many of them devised by the author) employed in animal experimentation. Operative procedures, apparatus and anatomic approaches are completely and beautifully illustrated in 892 figures, including 55 color plates. In addition there are excellent chapters on shop work, including the basic principles of glass blowing and metal work. There is also a short chapter on photography.

Since this is not a text in pharmacology but rather a laboratory manual that poses pertinent questions without answering them, it cannot be recommended to the general medical profession. As a laboratory guide, a more discriminating selection of a few fundamental experiments in connected sequence might better have served the purpose than the collection of 217 oft-repetitive exercises that the author has assembled for choice. The chapters on prescription writing and materia medica are well written and profusely illustrated. Since this book must necessarily be used in conjunction with a systematic text in pharmacology, a much smaller and more compact book might be more appropriate for student use.

J. C.

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HANDBOOK OF SKIN DISEASES. By LEON HUGH WARREN, B.A., M.D., M.Sc. (MED.), Formerly Instructor in Dermatology and Syphilology at the School of Medicine, Temple University; Acting Assistant Surgeon (Dermatology) in the Office of Dermatoses Investigations of the United States Public Health Service, etc. With a Foreword by FREDERICK K. WEIDMAN, M.D. Pp. 321. New York: Paul B. Hoeber, Inc., 1940. Price, \$3.50.

THIS little book fills the gap which exists between bulky texts on dermatology and the quiz compend. The author has acted most sensibly in not pretending to give complete descriptions of dermatoses where such are impossible except in ponderous volumes replete with illustrations and careful descriptions. The merit of this book consists in that the author has indicated the nature of the various dermatoses to a large extent in terms of the pathologist, thus informing the practitioner and the pathologist as to the general setting of such dermatoses in the scheme of medical disease. This is what such specialists desire, rather than to master the intricacies of the dermatologic specialty, such as is required by the formal texts.

To the specialist the book is of value because the recent advances in dermatology have been collected and made available in short form. For the dermatologist who has not had adequate contact with such items the handbook serves as a most useful aid. In this respect it surpasses quiz compends of the conventional type, which are planned rather for the medical student. However, the booklet should be of service to students also, but only in conjunction with their lectures and clinics.

The arrangement of the dermatoses in alphabetical order facilitates ready reference, as in an encyclopedia; this is supplemented by an index remarkably complete and detailed—34 pages in a book of 321 pages.

Therapy is covered with particular respect to physical therapy and other of the more modern modalities. Of course, all of this would be impossible



in a small book had the author not resorted to telegraphic style, and the latter will no doubt appeal strongly to the busy practitioner who needs only a catch word here and there to refresh his memory, or have suggestions offered to him. In short, the author's handbook should fill a definite want for practitioners, dermatologists and students.

F. W.

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A TEXT-BOOK OF OCCUPATIONAL DISEASES OF THE SKIN. By LOUIS SCHWARTZ, M.D., Medical Director, U. S. Public Health Service, in charge of Dermatoses Investigations, Washington, D. C.; Lecturer, Department of Dermatology and Syphilology, New York University, etc., and LOUIS TULIPAN, M.D., Clinical Professor of Dermatology and Syphilology, New York University College of Medicine; Consulting Dermatologist, Manhattan General Hospital, etc. Pp. 799; 116 illustrations. Philadelphia: Lea & Febiger, 1939. Price, \$10.00.

THIS work is a valuable contribution to American medical literature and an indispensable manual for those concerned with industrial diseases, including others than those of the skin. It is better systematized, more inclusive of the literature, but not as well indexed as its predecessor, Prosser White's "Dermatergoses." Throughout the work, the authority especially of the senior author, widely known to specialists in this country for his invaluable contributions to this field, is easily recognized. The first-hand descriptions of the manufacturing processes from which occupational dermatoses arise, lends a vividness and realism to the text which carries it beyond the limited confines of merely descriptive dermatology. The work can therefore be a volume of reference for all physicians concerned in industrial medicine, as well as for the dermatologist.

The book comprises 45 chapters, ranging from a brief discussion of workmen's compensation laws in relation to dermatoses, to an analysis of skin hazards in 74 occupations. The chapter on diagnosis is materially, and perhaps not advantageously, shortened by assigning to the dermatologist without differential description such conditions as seborrheic dermatitis, impetigo contagiosa and neurodermatitis, which so frequently defeat the industrial physician and the compensation authority in their encounters with industrial dermatology. Much emphasis is laid on patch-testing and many useful notes on its application with some regard for contributing influences such as perspiration, oiliness, dryness, friction and so forth are provided. Methods of investigation and prevention are briefly discussed and are recapitulated with specific application in many of the ensuing chapters on special industrial irritants. So far as the Reviewer could ascertain, with a limited knowledge of industrial processes but some contact with the problems of industrial dermatology, this work is an encyclopedic catalogue in which at one point or another practically everything that could be conceived as responsible industrially for injury to the skin receives at least brief, and usually illuminating, mention.

What has in the past been a notable deficiency in practical industrial work and in the field of industrial dermatology, is still recognizable, the Reviewer believes, in this book; that is, a lack of adequate discussion and analysis of the host factors so to speak, in the development of occupational dermatitis. The disposition is perhaps natural, to regard the offending substance as overwhelmingly the major part of the picture. A study of the human subject notably from such aspects as constitutional make-up and predisposition, physiologic and pathologic structural and functional abnormality, dietary, climatic and economic and psychologic components has yet to appear. Prosser White, in some of his discussions of industrial dermatology, foreshadowed the need for ultimate comprehension of the collateral influences which play a part and form the background of the irri-

tability of the skin. Industrial dermatology thus studied will be more than a descriptive catalogue of the action of individual irritants and will become an illuminating field for the interpretation of skin and general physiology. The interrelation between allergy and infection, infection-sensitization complexes, interplay between sensitizing contact factors and sweat, sebaceous, vascular and nervous mechanisms of cutaneous disease will go far towards broadening the preventive outlook as well as the actual management of occupational skin diseases.

This suggestion for a greater completeness and a more broadly medical treatment is not offered with any intent to minimize the distinction of the authors' work.

J. S.

SKETCHES IN PSYCHOSOMATIC MEDICINE. By SMITH ELY JELLIFFE, M.D., Consulting Neurologist to Manhattan State and Kings Park Hospitals, New York. Pp. 155; 10 figures. New York: Nervous and Mental Disease Monographs, 1939. Price, \$3.00.

THE author, one of the first and most distinguished of American psychoanalysts, has long maintained that medical and surgical treatment of physical conditions resulting from prolonged emotional strain, may be attended by dire consequences, unless proper psychologic preparation has been given. From his voluminous writings, the following selection of monographs are offered in support of that contention: What Price Healing?; Psychopathology and Organic Disease; The Death Instinct in Pathology; Dupuytren's Contracture; The Psyche and the Vegetative Nervous System; The Bodily Organs and Psychopathology; The Skin, Nervous System and the Bath; Neuropathology of Bone Disease; Psychoanalysis and Myopia; The Ecological Principle in Medicine. In recent years, much has been written in corroboration of such findings. A bibliography and index are included.

N. Y.

THE PROCEEDINGS OF THE CHARAKA CLUB, VOL. IX. Pp. 204; illustrated. New York: RICHARD R. SMITH for The Charaka Club, 1938.

THE ninth volume of the Proceedings of this egregious organization is indeed illustrative of the versatility and virtuosity of its members. Its 30 or more contributions (delivered mostly between 1934 and 1937) range through serious articles on medical history and medical biographic sketches to non-medical essays and poems by physician members. Almost an equal number of unpublished contributions during the same period are listed, some of which, to judge from the titles and from one pungent article here printed, look as if they also would make very entertaining reading.

E. K.

PATHOLOGY. An Introduction to Medicine and Surgery. By J. HENRY DIBLE, M.B. (GLAS.), F.R.C.P. (LOND.), Professor of Pathology in the University of London (The British Post-Graduate Medical School); Late Professor of Pathology at the London School of Medicine for Women, etc., and THOMAS B. DAVIE, B.A. (CAPE), M.D. (L'POOL), M.R.C.P. (LOND.), Professor of Pathology in the University of Liverpool; Late Professor of Pathology in the University of Bristol. Pp. 931; 374 illustrations, including 8 plates in color. Philadelphia: The Blakiston Company, 1939. Price, \$10.00.

In this book the authors have endeavored "to present pathologic changes to the student in a series of *processes* going on in the living body and leading to certain consequences—signs, symptoms, functional changes and morbid anatomical results." Possibly because of these aims, admirable though they are, the several parts of the book are of unequal merit. There is an

## BOOK REVIEWS AND NOTICES

overlong discussion of subject matter usually included in textbooks on bacteriology and immunology; and in consequence, many subjects usually discussed in parts devoted to special pathology receive scant notice. On the other hand, a number of chapters in the field of general pathology (e. g., fatty changes) are fully and well treated.

There are no references to original sources, though names of prominent investigators are used. This omission, in the Reviewer's opinion, is a mistake; medicine is a graduate study and the student should be directed to the literature lest he develop a mistaken sense of dependence on the authority of the textbook.

Taking the work as a whole, it does not appear to be as suitable for courses in pathology in American universities as several texts now available.  
B. L.

**DIAGNOSTIC SIGNS, REFLEXES AND SYNDROMES (STANDARDIZED).** By WILLIAM EGBERT ROBERTSON, M.D., F.A.C.P., Visiting Physician, Medical Division, Philadelphia General, St. Luke's and Children's and Northeastern Hospitals, and HAROLD F. ROBERTSON, B.S., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Assistant Visiting Physician, Medical Division, Philadelphia General and Methodist Hospitals. Pp. 309. Philadelphia: F. A. Davis Company, 1939. Price, \$3.50.

Nor just a routine collection of signs, largely eponymic (although a mal-  
evolent State-Board medical examiner might find here much devastating material), but a careful compilation of diagnostic aids, well tintured by the clinical experience of the compilers. In alphabetical order are given not only the signs, but diseases in which they occur and organs to which they are referred. The work should be helpful for reference by physicians and students.  
R. K.

**LEHRBUCH DER AUGENHEILKUNDE.** By DR. ERNST FUCHS, Sechzehnte, vermehrte und verbesserte Auflage neu bearbeitet, von DR. ADALBERT FUCHS, a. o. Professor der Augenheilkunde an der Universität in Wien. Pp. 904; 362 text illustrations and 5 colored plates. Wien: Franz Deuticke, 1939. Price, Paper, M. 27; Bound, M. 30.

For many years Fuchs' text book translated by Duane was the standard American text. When Dr. Duane died this book rapidly went out of print and copies are being sold at a premium. Although this present text is in German, it retains all the best features of the English translation and brings the subject matter up to date. It will be a valuable addition to the libraries of all ophthalmologists who read German fluently.  
F. A.

**CÆSAREAN SECTION. Lower Segment Operation.** By C. McINTOSH MARSHALL, F.R.C.S. (ENG.), Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. Pp. 230; 107 illustrations and 2 colored plates. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.50.

This volume deals with the operative aspect of the intraperitoneal lower segment Cæsarean section operation. It includes an extensive review of the literature and the author's experience, based upon the performance of 250 operations. The history of the operation is well treated in the introductory chapter. The remaining chapters deal with anatomy, incisions, anesthesia, the technique of the lower segment operation, infection, hemorrhage, the use of oxytocics, the place of the operation in cases of placenta prævia, the difficulties and dangers of the operation and the authors results. The book is well arranged and profusely illustrated. There are numerous

paragraph headings which make it a good reference volume. The bibliography is very extensive, but the lack of titles detracts greatly from its value for the research investigator, in the opinion of the Reviewer. For the practicing operating obstetrician the volume should be an extremely one. D. M.

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FUNDUS ATLAS. Stereoscopic Photographs of the Fundus Oculi. By LOUIS BOTHMAN, B.S., M.D., F.A.C.S., Clinical Professor of Ophthalmology, The University of Chicago; Associate Ophthalmologist, St. Luke's Hospital, Chicago, and REUEL W. BENNETT, Photographer for the Division of Ophthalmology, The University of Chicago Clinics. Pp. 50; 50 original stereoscopic photographs. Chicago: The Year Book Publishers, Inc., 1939. Price, \$17.00.

THIS collection of fifty plates for use in a stereoscope will be found useful for teaching ophthalmoscopic diagnosis. The plates were made from fundus photographs taken with the Nordensen camera and magnified three or more times the size of the original negatives. On each card is a history of the case and a description of the various details which are to be found. F. A.

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THE RISE OF EMBRYOLOGY. By ARTHUR WILLIAM MEYER, Professor of Anatomy, Emeritus, Stanford University. Pp. 367; 95 illustrations. Stanford University: Stanford University Press, 1939. Price, \$6.00.

THE author has elected to treat his subject by tracing separately the history of the great problems of embryology, *e. g.*, spontaneous generation, the ovum, the spermatozoön, and so on. This method has obvious advantages, but it scatters the work of a single investigator, perhaps failing to give a picture of the man and his accomplishments. Of special interest to the physician is a chapter on the development of visual and technical aids and another dealing with malformations. Quotations are freely used throughout the book, which is well illustrated and closes with an excellent 19-page bibliography. The index, however, is regrettably brief. H. S.

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ATLAS OF SURGICAL OPERATIONS. By ELLIOTT C. CUTLER, Moseley Professor of Surgery, Harvard University and Chief Surgeon of the Peter Bent Brigham Hospital; Formerly Professor of Surgery, Western Reserve University, and Director of Surgery of the Lakeside Hospital, and ROBERT ZOLLINGER, Associate Professor of Surgery, Harvard University, and Senior Associate in Surgery at the Peter Bent Brigham Hospital. Pp. 181; 84 plates. New York: The Macmillan Company, 1939. Price, \$8.00.

THIS is a unique atlas. There is a chapter on surgical technique, one on anesthesia and one on pre- and postoperative care. The remainder of the volume consists of 84 large plates showing the technique of a variety of operations, with a page opposite each plate in which there is briefly discussed the indications for operation, the preoperative preparation, the anesthesia, the position of the patient, the operative preparation, the incision and exposure, the details of operation and the postoperative care. The illustrations are done in black and white line drawing. They are exceedingly simple yet nevertheless very well done.

This volume will prove very useful to all surgeons, whether young or old. Within a page or two one can obtain knowledge of certain standardized surgical procedures. The many illustrations on a single plate make it possible to visualize the steps of the operation from beginning to end on a single page.

Drs. Cutler and Zollinger are to be congratulated on the splendid piece of work they have done, but the Reviewer must also congratulate the artist who has so acceptably depicted the operative procedures. Every surgeon would not do every operation in the same way, but this is a volume that every young surgeon can use and follow with benefit to himself and to the patient. Many of the more competent technicians in surgery could well heed the constant admonition on the gentle handling of tissues, the necessity of completing the hemostasis, and the necessity of adequate exposure.

I. R.

**A TOPOGRAPHIC ATLAS FOR X-RAY THERAPY.** By IRA I. KAPLAN, B.S., M.D., Director, Radiation Therapy Department, Bellevue Hospital; Director, Division of Cancer, Department of Hospitals, City of New York, etc., and SIDNEY RUBENFELD, B.S., M.D., Associate Visiting Radiation Therapist, Bellevue Hospital; Instructor in Surgery, New York University Medical College, etc. Pp. 120; 55 full page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, \$4.00.

This atlas is admirably suited for teaching purposes. It contains 55 excellent diagrammatic illustrations dealing with different diseases. Each clearly presents the normal visible anatomic landmarks and the palpable internal landmarks. The diseased organs are outlined within the body. The relative size, number, and position of each treatment cone used is clearly indicated. Printed in outline form opposite each illustration is a verbal description of each illustration. The fundamental mechanics of applying Roentgen therapy are all referred to, except physical factors of dosage. The authors have deliberately avoided consideration of the latter, so that the reader will not find any mention of the amount and quality of radiation to be used in various conditions.

P. H.

**ARGYRIA. The Pharmacology of Silver.** By WILLIAM R. HILL, M.D., Instructor in Dermatology and Syphilology, University of Pennsylvania, and DONALD M. PILLSBURY, M.A., M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania. Pp. 172. Baltimore: The Williams & Wilkins Company, 1939. Price, \$2.50.

This little monograph covers more than the subject indicated in the title: there are chapters on the history of argyria, its absorption and excretion, its deposition in tissues, the pharmaco-physiologic effects, the diagnosis and treatment, an analysis of reported cases, and its treatment. Argyria of the eye and industrial argyria also occupy chapters. There are 601 references and there are complete author and subject indexes. Most useful, too, is a list of proprietary silver compounds; it is surprising that they should number a hundred or more.

The subject is treated from the biologic viewpoint throughout, with attention to detail, dispassionately and judicially. The authors have rendered a distinct service in bringing the subject down to date in such a complete, authoritative and scientific manner.

F. W.

## NEW BOOKS.

*On Oxidation, Fermentation, Vitamins, Health and Disease.* (The Abraham Flexner Lectures, Series No. 6.) By ALBERT V. SZENT-GYÖRGYI, M.D., PH.D. (CANTAB.) D. H. C., Prix Nobel, Professor of Medicine and Organic Chemistry. University of Szeged. Pp. 109. Baltimore: The Williams & Wilkins Company for Vanderbilt University, 1939. Price, \$2.00.

*New Facts on Mental Disorders.* Study of 89,190 Cases. By NEIL A. DAYTON, M.D., M.C., Director, Division of Statistics and Director, Division of Mental Deficiency, Massachusetts State Department of Mental Health, etc. Pp. 486; 110 graphs; 84 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, \$4.50.

*Pneumoconiosis (Silicosis). The Story of Dusty Lungs.* A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 56 and Appendix (47 pages); illustrated. New York: John B. Pierce Foundation, 1940. Price, \$1.00.

*Sex and Life: Forty Years of Biological and Medical Experiments.* By EUGEN STEINACH, M.D., Ph.D., Formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by JOSEF LOEBEL, M.D. Pp. 252; 67 illustrations (many in color). New York: The Viking Press, 1940. Price, \$3.75.

*The Medical Clinics of North America, Vol. 24, No. 1 (Chicago Number—January, 1940).* Pp. 283; 37 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This Chicago number presents a timely symposium of 14 articles (comprising about two-thirds of the volume) on various practical aspects of geriatrics. As a useful complement to the less clinical aspects of the subject comprised in the recent volume on Problems of Ageing (Baltimore, The Williams & Wilkins Company, 1939), this part of the volume might well have been even further amplified.

*The Specific Therapy of the Pneumonias.* By JESSE G. M. BULLOWA, M.D., Clinical Professor of Medicine, New York University College of Medicine. (Beaumont Lecturer for 1939.) Pp. 80; illustrated. (Reprinted from the Journal of the Michigan State Medical Society, July-August, 1939.)

*Clinical Toxicology.* By CLINTON H. THIENES, M.D., Ph.D., Professor of Pharmacology and Head of the Department of Pharmacology, School of Medicine, University of Southern California, Los Angeles; Attending Pathologist (Toxicology), Los Angeles County Hospital. Pp. 309; 7 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$3.50.

*Orthopedic Operations.* Indications, Technique and End Results. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City. Pp. 766; 865 illustrations on 322 figures. Springfield, Ill.: Charles C Thomas, 1940. Price, \$9.00.

*Le Débit Cardiaque. Etudes Expérimentales et Cliniques.* By JEAN LEQUIME, Agrégé de l'Enseignement supérieur Assistant à l'Université de Bruxelles. Preface by Professeur Paul Govaerts. Pp. 223; illustrated. Paris: Masson et Cie, Editeurs, 1940. Price, 40 francs.

*Das Anlitz der Blindheit in der Antike.* Eine medizinisch-kulturhistorische Studie. By A. ALBERT M. ESSER, Dr. med et phil. Pp. 178. Stuttgart: Ferdinand Enke, 1939. Price, Paper, Rm. 9.50; Bound, Rm. 11.00.

*Carbohydrate Metabolism.* Four pages presented in a Symposium held at the meeting of the American Physiological Society at Toronto, Canada, April 29, 1939. Chairman: PROFESSOR C. H. BEST. (Reprinted from Endocrinology, Vol. 26, No. 2, February, 1940.) Pp. 66; illustrated. Menasha, Wis.: The George Banta Company, 1940. Price, \$1.00.

This consists of reprints of four interesting papers presented in a Symposium of the American Physiological Society. They deal with a résumé of each author's experimental work, in relation to the work of others, on the rôle of enzymes, the liver, the adrenal cortex, and the pituitary in carbohydrate metabolism. I. Z.

*Directory of Medical Specialists.* Certified by American Boards. PAUL TITUS, M.D., Directing Editor. Pp. 1573. New York: Columbia University Press, 1940, for The Advisory Board for Medical Specialties. Price, \$3.50.

- Injuries of the Skull, Brain and Spinal Cord.* Neuro-Psychiatric, Surgical, and Medical-Legal Aspects. Edited by SAMUEL BROCK, New York University. Contributors: B. J. ALPERS, ABRAHAM BLAU, K. M. BOWMAN, SAMUEL BROCK, JEFFERSON BROWDER, BRONSON CROTHERS, L. M. DAVIDOFF, T. K. DAVIS, CHARLES DAVISON, C. G. DYKE, C. A. ELSBERG, A. R. ELVIDGE, E. D. FRIEDMAN, F. C. GRANT, C. C. HARE, G. B. HASSIN, MOSES KESCHNER, M. M. PEET, W. R. RUSSELL, PAUL SCHILDER, C. P. SYMONDS. Pp. 632; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, \$7.00.
- Non-Profit Hospital Service Plans.* Historical and Critical Analysis of Group Hospitalization, a non-profit, non-political application of the principle of insurance to the purchase of hospital care. By C. RUFUS ROREM, Ph.D., C.P.A., Director, Commission on Hospital Association, Chicago. Pp. 130. Chicago: Commission on Hospital Service, 1940. Price, 50¢.
- The Medical Career and Other Papers.* By HARVEY CUSHING. Pp. 302. Boston: Little, Brown & Co., 1940. Price, \$2.50.
- Preclinical Medicine.* Preclinical States and Prevention of Disease. By MALFORD W. THEWLIS, Attending Specialist, General Medicine, United States Public Health Hospitals, New York City; Special Consultant, Rhode Island Department of Public Health, etc. Pp. 223; 12 figures. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.00.
- Heil Hunger! Health Under Hitler.* By DR. MARTIN GUMPERT, Translated from the German by MAURICE SAMUEL. Pp. 128. New York: Alliance Book Corporation, 1940. Price, \$1.75.
- Syphilis and Its Accomplices in Mischief: Society, the State and the Physician.* By GEORGE M. KATSAINOS, M.D. Pp. 554; Athens, Greece: Privately Printed, 1939. Price, \$4.75. (Author's address, 132 Hemenway St., Boston, Mass.)
- Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases.* By Egon BRUNN. Pp. 229; 49 illustrations. Copenhagen: Einar Munksgaard. Price, Dan. Kr. 24.00.
- Shock, Blood Studies as a Guide to Therapy.* By JOHN SCUDDER, M.D., Med. Sc.D., F.A.C.S. From the Surgical Pathology Laboratory of the College of Physicians and Surgeons, Columbia University, and the Department of Surgery, the Presbyterian Hospital, New York City. Pp. 315; 58 illustrations, and 5 plates (3 in color). Philadelphia: J. B. Lippincott Company, 1940. Price, \$5.50.
- Modern Diabetic Care.* Including Instructions in the Diet and the Use of the Old and New Insulins. By HERBERT POLLACK, A.B., Ph.D., M.D., Instructor in Clinical Medicine, Cornell Medical College; Chief of the Diabetic Clinic, Mt. Sinai Hospital, New York City, etc. Pp. 216. New York: Harcourt, Brace & Co., 1940. Price, \$2.00.

## NEW EDITIONS.

- A Textbook of Surgery.* By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from Lectures and Other Writings of 23 Members of the Surgical Department of The Harvard Medical School. Pp. 1272; 530 illustrations by Willard C. Shepard. Fourth Edition. Springfield, Ill.: Charles C Thomas, 1940. Price, \$8.00.
- The Management of Obstetric Difficulties.* By PAUL TITUS, M.D., Obstetrician and Gynecologist to The St. Margaret Memorial Hospital, Pittsburgh; Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, and to The Homestead Hospital, Homestead, Pa. Pp. 968; 368 illustrations and 5 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$10.00.

# PROGRESS OF MEDICAL SCIENCE

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## GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF  
CHARLES C. NORRIS, M.D.,  
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,  
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

AND  
FRANK B. BLOCK, M.D.,  
SURGEON, JEWISH HOSPITAL, PHILADELPHIA

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### ENDOMETRIOSIS.

ALTHOUGH it is less than 20 years since Sampson<sup>13</sup> presented his outstanding work on perforating hemorrhagic cysts of the ovary, the interest aroused in this fascinating subject continues unabated. Of the various names suggested for this condition the term "endometriosis" has been generally accepted, signifying a disease in which non-malignant but often invasive growths are found which are composed of gland-like structures resembling endometrial glands. An important characteristic of these lesions is that, like endometrium, they react to hormonal stimulation from the ovary, enlarging during the congestive premenstrual phase of the menstrual cycle and decreasing in size during the resting phase. While at first these growths were found only in the pelvic cavity, principally in the ovary, further investigation has shown that they may involve various structures both within and outside the pelvis. From the clinical aspect the subject has been well reviewed by Counsellor<sup>5</sup> of the Mayo Clinic, with a discussion of the various hypotheses concerning the pathogenesis of this condition. He has grouped these hypotheses into three classes: 1, embryonic; 2, metaplastic; and 3, migratory. The embryonic hypothesis would include the Wolffian theory of von Recklinghausen and the Muellerian hypothesis favored by Cullen, in each of which the growths are supposed to arise from embryonic structures. These theories can only explain the endometriomas in the immediate vicinity of the uterus where these embryonic rests could exist and Counsellor believes that these theories at the present time are of historical interest only. Concerning the metaplastic hypotheses, he recalls that Iwanoff first suggested a serosa-epithelial metaplasia of the peritoneum, which at present is usually known as the theory of Meyer who advanced it further. According to this theory, under the influence of an inflammation or of an ovarian hormonal action, the pelvic peritoneum might form tubular invaginations which would sink more or less deeply into the tissues of subjacent organs. At the same time, the flat endothelium of the involved peritoneum might become transformed into columnar epithelium, thus producing an adenomatous appearance. Although



the common celomic origin of the peritoneum, the ovary and the Mullerian ducts might be consistent with this hypothesis, it seems that they assume profound histologic and physiologic changes for adult peritoneum. While it is clearly established that the ovarian hormones have an important effect on fully developed endometriomas, it is not established that they might initiate the development of these lesions.

The final or migratory hypothesis assumes that the endometrial tissue in endometriosis has its origin in the uterine mucosa, although it may become transplanted in several ways. It is generally accepted, as suggested by Cullen, that adenomyomas of the uterus illustrate an invasion of the uterine musculature by its endometrial lining, or invasion by contiguity. Sampson's hypothesis of retrograde menstruation with possible ineubation of endometrial implants in the ovary is perhaps the most generally accepted theory. In operations performed during the menses, blood has frequently been seen coming from the tubes. However, the grafting in the pelvis of devitalized endometrial elements found in menstrual blood is speculative and this hypothesis does not explain endometriosis of the groin or of the umbilicus. Another subdivision of the migratory hypothesis is that of lymphatic metastasis. According to this theory it is assumed that during menstruation, by virtue of the indefinite limit between endometrial tissue and the subjacent tissues, epithelial elements may enter open lymphatic vessels and be carried to the subscroal lymphatics or to the uterosacral ligaments, the broad ligaments, the ovaries, the round ligaments or the abdominal wall. The known lymphatic drainage of the uterus enables the tracing of a possible course to all of the locations in which endometriosis has been seen, including laparotomy scars. Counseller believes that this theory explains the histopathologic phenomena in endometriosis more adequately than any other.

Endometriosis is an extremely important disease of young women and its most predominant symptom is dysmenorrhea of an acquired or progressive type. Vesical and rectal pain superimposed upon dysmenorrhea is almost always diagnostic, while diffuse pelvic soreness, brought about by walking or jarring of the pelvis in any way, is also suggestive. He believes that in the majority of cases radical surgical treatment should be employed, in fact radical treatment was carried out in about 80% of a series of 884 cases at the Mayo Clinic. Cases in which conservative procedures are to be carried out must be very carefully selected if recurring lesions and subsequent treatment are to be avoided. The percentage of recurrences will be reduced by limiting conservative treatment to those in which relatively few surgical procedures will be required to remove the disease. He believes that it is safer to err on the side of radicalism than to attempt preservation of ovarian function in those cases in which there is some involvement of both adnexa or in which there is considerable involvement of one side and the adjacent uterine wall. At the Clinic they feel that the upper age limit for conservative procedures is between 37 and 40 years but the extent of the lesions and their location are more important in selecting the type of operation than is the age of the patient. It has been their observation that when it is necessary to perform radical hysterectomy for endometriosis before the menopause, the patients do not experience the severe menopausal symptoms that those patients do who undergo a similar

operation for conditions other than endometriosis. They have not been able to show that conservative procedures are of much value in the elimination of sterility since only 7 of the 55 patients whom one could reasonably expect to become pregnant did become so; in fact, pregnancy can only be expected in those cases in which the disease is limited to one side or to a relatively few implants which can be excised. While it is possible to castrate these patients by irradiation rather than by operation, it is his belief that patients under the age of 40 should be submitted to surgical treatment because it is impossible to determine clinically whether complete cessation of ovarian function is advisable. Furthermore, it is much wiser to know whether there is any other associated pathologic condition of the pelvic organs before submitting the patient to castration by radium or Roentgen rays. The one exception to this rule may be a large adenomyoma of the rectovaginal septum which cannot be removed surgically without considerable risk of producing a rectal fistula.

In analyzing his series of 112 cases, Allen<sup>1</sup> was impressed by several features of the disease, namely, the high incidence of menstrual irregularities, the regular appearance of associated benign uterine tumors, the marked prevalence of relative sterility and the wide distribution of the lesions. The marked irregularities in the menstrual habit suggests to him a glandular imbalance and would explain those instances of irregular bleeding occurring in patients in whom the lesions were insignificant or so located that they could not very well have been the mechanical cause of change in the menstrual flow. Bleeding occurred from the endometrium in all stages of development, although that representing the Swiss cheese type of hyperplasia was the most common. The high incidence of fibromyomas in this series was noteworthy and on first thought might explain the increase in bleeding and high incidence of sterility but it seems more logical to him to include these masses of functionless tissue as an end-result of hormonal cell stimulation due to an underlying glandular dysfunction. The wide distribution of the lesions necessitates the acceptance of either the Sampson theory or the theory of metaplasia, the latter pointing to some increased hormonal activity. The high incidence of sterility, in spite of patent tubes and potent mates, suggests some disturbance in physiology rather than mechanical interference since sterility is a common result of glandular imbalance characterized by menstrual irregularities. On the whole, therefore, he feels that endometriosis is a manifestation of cellular metaplasia caused by glandular dysfunction and until we know more about their action prolonged administration of potent glandular products may be fraught with danger.

Of 375 cases of endometriosis reported by Pemberton,<sup>10</sup> 66% had radical operations and 34% were treated by conservative methods, either operative or irradiation. There was only one death in the whole series. Of the cases treated by conservative measures, 29% needed further treatment. He believes that Roentgen rays should be used for secondary treatment if the chief symptom is menorrhagia or dysmenorrhea but not under other circumstances. He is cautious in the use of radium in these secondary cases because the intestine may be adherent to the uterus and therefore may be devitalized by radium placed within the uterus. Pregnancy occurred after conservative operation in 19 of

the 76 patients in whom it might have been expected, so that for this reason alone he believes that a conservative operation will often be indicated. If pregnancy is not a factor in the decision as to the type of operation he feels that it is better to perform a hysterectomy with bilateral oöphorectomy because of the high percentage of failure of the conservative operations.

In contrast to the radical views concerning treatment which have thus far been presented is the report from the Lahey Clinic of a small series (43 cases) reported by Cattell and Swinton.<sup>4</sup> They have found that a preoperative diagnosis of endometriosis is seldom made; 3 such cases were recognized before operation in their series and several more had this tentative diagnosis, one was an obvious lesion of the round ligament while the other two caused obstruction of the sigmoid at the time of menstruation. Ovarian endometriosis will always be difficult to differentiate from chronic pelvic inflammation but such symptoms as abnormal menstruation, sterility, acquired dysmenorrhea and lower abdominal pain should make one consider endometriosis particularly when associated with a fibroid uterus or malpositions of the uterus which interfere with its drainage. They agree with the preceding authors that the treatment of this condition depends on the extent and location of the lesion, the age and the general physical condition of the patient, but complete involvement of the ovaries and the necessity for castration have been rare in their experience. Three of their patients have had children following the removal of one ovary for endometriosis. They feel that the removal of all ovarian tissue in young women is a very serious matter and is not warranted in this disease where local excision can be performed. In women over 40 years of age supravaginal hysterectomy with removal of the tubes and ovaries is indicated. In poor risk patients, it is to be remembered that castration will cause the lesion to recede and usually relieve symptoms. In this group the production of an artificial menopause through the use of Roentgen ray therapy should be considered. In the rectovaginal group where intestinal obstruction has not occurred, the disease can be relieved by local excision followed by the production of an artificial menopause. Where intestinal obstruction has occurred, the obstruction must first be relieved by colostomy. This colostomy should be done in such a manner that it can later be closed, since following the removal of the ovaries the lesion will regress and the obstruction will be relieved. In bladder endometriosis, the production of an artificial menopause will cause the lesion to disappear. In endometrial tissue in the appendix, the removal of that organ will end all trouble while local excision will usually cure other types of endometriosis. In a word, they have found that the end results after both conservative and radical operations are satisfactory in properly selected cases.

**Endometriosis of the Bladder.** In a review of reported cases of bladder endometriosis, including one of his own, Henriksen<sup>6</sup> has found that a fairly constant symptom complex presents itself, although a few have been asymptomatic from a urinary standpoint. In the majority of the cases frequency, dysuria and hematuria appear several days before menstruation, persist during the flow and continue for a day or even a week after its cessation. The course of the disease is chronic, starting first with a slight discomfort, which is constant but not aggra-

vated by the menstrual periods, though later the clinical picture changes, the following description being fairly typical. Increased frequency of urination both by day and by night is the most common complaint and as a rule completely disappears between the periods. Dysuria varies but usually occurs at the end of micturition, more as a sense of discomfort than as actual pain. Hematuria, because of its microscopic nature, is rarely noted by the patient and is present only during menstruation or just preceding it. There is a marked variation in the severity of the symptoms depending on the size and topographic location of the tumor within the bladder, as well as the degree of tissue reaction during the menstrual period. When the ureters are encroached on there is the added symptom suggesting kidney involvement. The youngest patient in the group was 19 years of age. There is apparently, however, a predilection for the decade between 35 and 45 years and except for one case, all have occurred during menstrual life. As a rule the tumors are located within the floor of the bladder, just above or between the ureters, peculiarly more toward the right side. They are rarely found in the vertex and though they may involve the trigone, the involvement is through extension. The size of the tumors is fairly constant, being generally between 2 and 4 cm. and they usually present a distinctly nodular surface. The treatment of this tumor cannot be prescribed dogmatically. The size, location, age and general condition of the patient are the deciding factors as to which of the two possible therapeutic procedures is best suited. Complete excision is the method of choice in young women desirous of children and in whom the margin of bladder tissue safety is sufficient, while castration is done, either by operation or by irradiation, in patients near the menopause or in whom the growth is too extensive for excision, or when the general condition of the patient contraindicates surgical measures. Since there are cases presenting an atypical picture, this tumor may easily be mistaken for a malignant lesion of the urinary bladder.

In presenting a complete history of a case of this disease, beautifully illustrated with colored plates, Phillips<sup>11</sup> reviews 29 cases previously reported in the literature. He believes that the incidence of bladder endometriosis is far greater than reported and would be found if the cystoscope were used more frequently in diagnosis. The possibility of the disease should always be thought of in a patient suffering from frequency of urination, dysuria and hematuria. When this triad is cyclical and is exacerbated during the period and one finds on cystoscopic examination that "blue-black" cysts and "endometriotic edema" are present, the diagnosis of endometriosis of the bladder is certain. He believes that the method of choice in treatment is by the induction of an artificial menopause with Roentgen ray. Surgical interference, however, is indicated in those few cases in which the patient is considerably under the menopause age and is desirous of children. In reporting a single case of his own, Reynolds<sup>12</sup> corroborates practically everything that Phillips has stated and agrees with him as to the choice of treatment.

**Endometriosis of the Umbilicus.** Presenting 2 cases of his own and collecting over 70 cases from the literature, Weller<sup>15</sup> states that the umbilicus cannot be regarded as a rare location for endometriosis. In this location smooth muscle is not often present so that the term "adenomyoma" is inappropriate. The sweat glands, which have been men-

tioned repeatedly in connection with umbilical endometriosis, have no part in the genesis of this condition. The origin of the disease in this location is explainable only with the greatest difficulty under the implantation and metastasis theories but is readily understandable under the various modifications of the serosal theory. For those especially interested in umbilical endometriosis, the article of Boggs<sup>2</sup> is heartily recommended since in addition to reporting his own case very well, 96 other cases from the literature are reported chronologically and a complete bibliography of the subject is appended. He reminds us that this condition always occurs during the years of ovarian activity and the cyclic nature of the symptoms, corresponding to the menstrual periods, will usually suggest endometriosis. The symptoms include the secretion of a blood-tinged fluid from the navel and pain, tenderness, swelling, itching and bluish discoloration. The tumors usually reach full size in from 2 to 6 months, ranging from 1 to 3 cm. in diameter, occasionally reaching a diameter of 5 cm. These tumors must be differentiated from uterine fistulas, which also may produce menstruation. The treatment of choice is wide excision, the technique being that used for hernial repair. It is interesting to note that in the case he reports, the patient was an unmarried woman of 49 years who had had a hysterectomy 2 years previously. This was followed by a period of amenorrhea until menstruation from the umbilicus began, but she never had further vaginal bleeding.

**Rare Forms of Endometriosis.** A case of *endometrioma of the perineum* has been recorded by Maliphant<sup>8</sup> who presents 3 other cases collected from the literature. The case recorded occurred in a patient operated upon for a lacerated perineum. The day after operation she menstruated and 2 years later a tumor developed in the perineal scar which showed the typical structure of uterine mucosa. The history is very suggestive that this tumor was a true implant and that it had grown from a fragment of exfoliated uterine mucosa in the menstrual discharge.

At the Lahey Clinic according to Cattell,<sup>3</sup> 16.3% of the 104 patients with endometriosis had intestinal symptoms due to *involvement of the sigmoid and rectum*. The diagnosis is seldom made preoperatively but should be suspected when the obstruction is long standing and is worse at the time of menstruation, when there are associated pelvic findings and when the local lesion on examination by the sigmoidoscope and barium enema is not typical of carcinoma. The condition can usually be readily recognized at operation. Because of the complicating intestinal involvement, the operative treatment must be directed not only to the ovaries but to the intestinal lesions as well. It is sometimes necessary to resect the sigmoid but often removal of the ovaries is all that will be necessary since the growth will regress after the artificial menopause with its accompanying loss of ovarian hormone. In cases of severe intestinal obstruction due to this lesion, a temporary colostomy will have to be made.

Sehumann and Parke<sup>14</sup> report 2 cases in which endometriosis occurred in *laparotomy scars* and they comment that almost all of the reported cases follow a Cesarean section or pelvic laparotomy although several have followed an appendectomy. These endometriomas usually present themselves as fairly firm, nodular masses rarely larger than 3 or 4 cm.

in diameter, lying in the laparotomy scar and sometimes enlarge and even discharge blood at the menstrual period. They may or may not produce localized pain, are usually attached to the sheath of the rectus muscle and rarely penetrate the parietal peritoneum. They have found no report of a malignancy developing in an abdominal endometrioma. After a discussion of the theories of origin of these tumors, such as has been presented previously in this review, they conclude that the mechanical implantation theory of Sampson is the only logical explanation for the appearance of these implants in abdominal scars.

Three cases are reported by Neel<sup>9</sup> from the Mayo Clinic in which endometrial tumors were present in the *inguinal region*. In the first case, the menses were regular and without pain and there had been no previous operation. In the second case, a right herniorrhaphy had been performed 18 years previously and the incision had drained for 4 months. Pain and soreness in the inguinal region were more pronounced during menstruation. In the third case, an appendectomy had been done 17 years previously and for 2 years preceding admission the patient complained of pain over the lower right abdominal quadrant at each menstrual period, often persisting for 10 or 15 days after the period. Although these tumors, often called adenomyomas, may occur at any point in the round ligament from its uterine attachment to its termination in the labium majus, they are said to be 3 times as common in the extraperitoneal portion of the ligament as in the intraperitoneal portion and are usually found near the external inguinal ring. The frequency with which an inguinal hernia is associated is very striking. The diagnosis of a typical lesion should offer no difficulty. The presence of a more or less fixed, irreducible swelling in a woman in the child-bearing age, which is more prominent and more painful during each menstrual period, or is associated with discomfort which is more pronounced following the menstrual period, should lead one to suspect the true nature of the tumor. In one of the cases reported in the literature the patient complained of an abscess of the vulva which had been discharging for 2 years and which had caused throbbing pain during menstruation. In another case, the inguinal mass had been mistaken for a broken down lymph node and had been incised after which a sinus developed and blood had been discharged at each menstrual period. If the tumor is asymptomatic, the diagnosis will probably be made only by the pathologist.

The experimental production of *endometrial transplants in the lungs* of rabbits has been demonstrated by Hobbs and Bortnick.<sup>7</sup> These experiments have also demonstrated that endometrial tissue can be transported through the veins to the lungs. (They<sup>7</sup> have recorded the history of a woman of 42 which, while lacking positive proof, strongly suggests the diagnosis of endometriosis of the lung.—C. C. N.) Endometrial tissue has been demonstrated in the lumina of veins and lymphatics by other investigators and an abundance of information has been recorded from which one can deduce that uterine mucosal tissue must be transported through the lymph and blood vascular systems. With the fact established that such tissue is transported through these systems and that the tissue will grow in the lungs, they believe that it is logical to assume that uterine mucosa does occasionally become implanted in the lungs. It is also plausible that this tissue might rarely be found

in any organ in the body, since it may get into the left heart either by passing through a patent foramen ovale or by propagating through the capillaries of the lungs into the pulmonary veins and thence into the left heart. With this possibility of wide dissemination in mind, a credible theory for the explanation of vicarious menstruation becomes evident since it may be due to endometrial transplants in the area from which the periodic bloody discharge issues.

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### DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF

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### THE COSTS OF SYPHILIS.

To gain insight into the monetary needs for the effective control of syphilis, it is highly desirable to collate what information is available in the recent literature on the cost of syphilis. We must recognize that any attempt to determine and correlate these costs at present results only in a gross approximation. Such a compilation is of limited usefulness also, as the costs, both direct and indirect, vary from time to time and from locality to locality. Not only are the figures few and inaccurate, but the costs themselves are of an indefinable character. In the direct costs of medical care the proportion of the expenditure necessitated by the incidental finding of syphilis among the recipients of service is a fraction which defies calculation. The indirect costs are even more vague, and their extent is a matter of conjecture. In this attempt to assemble the most important of the available con-

tributions to this subject, we recognize the shortcomings of the data, as well as the deficiencies in the methods by which they were obtained.

Certain individuals in this country have been especially prominent in the effort to arrive at an idea of the costs of syphilis to the individual and to the community as a whole. Among them are Keidel<sup>18</sup> of Baltimore, Loeffler<sup>20</sup> of St. Louis, Bromberg and Davis<sup>5,9</sup> of Chicago, Brumfield<sup>6,40</sup> of Albany, N. Y., and his associates of Baltimore, Goldberg<sup>14a,b</sup> of New York, Rice<sup>34</sup> of the United States Public Health Service, and Nelson<sup>29a,b,c</sup> of Massachusetts. In keeping with the lack of definition of the costs of syphilis, some of these individuals criticize each other's methods of approach, but derive figures with a surprisingly similar trend.

The magnitude of the costs of syphilis can be surmised from the incidence and prevalence figures for this disease in the United States, as given by Vonderlehr, Usilton, and Nelson.<sup>29b,44,45,46</sup> On the basis of one-day cross-sections and other statistical determinations, it is now definitely known that the minimum number of persons in the United States constantly in need of medical care because of syphilis is near 683,000, or 4 per 1000 population. Furthermore, in the United States annually 500,000 cases of early syphilis seek authorized medical care. In addition, there is a large undetermined number of individuals acquiring the infection who neglect treatment until some late manifestation forces them to have attention.

Vonderlehr and Usilton (1938)<sup>46</sup> showed that "the probability of acquiring syphilis sometime in life is 1 out of 10." This statement is founded on the annual attack rate applied to 100,000 individuals born alive and followed throughout life. Although the annual attack rate seems low, when cumulated so as to indicate the probability of acquiring syphilis by a given age, it is found that one-tenth of the people before the attainment of the 50th year of life will have acquired syphilis, out of every 100,000 born alive. This rate is usually lower than that found on routine serologic examination of persons tested under the antenuptial physical examination laws, in industry or any random sample of the population. Vonderlehr and Usilton<sup>46</sup> give several reasons for these differences: *a*, Many persons in a random sample are still in danger of acquiring the infection, but have not yet acquired it; *b*, the blood test for syphilis becomes negative, either spontaneously or as the result of treatment in many infected persons; *c*, death removes from the population a high proportion of those who are infected.

Vonderlehr and Usilton also show that treatment decreases the probability of a disastrous outcome in syphilis, so that serious late manifestations, such as neurosyphilis and cardiovascular syphilis are greatly diminished.

**The Cost of Treatment of a Syphilis Patient.** In 1919 Stokes<sup>38</sup> estimated that for patients of moderate means, the fee cost or cost to the patient of treatment of secondary syphilis in private practice was seldom less than \$500. In complicated cases, of course, the expense was greater. He further stated that the patient acquired syphilis early in life, before the victim has reached an earning capacity which will enable him to cope with the situation. The result is he neglects it and loses the opportunity for cure for which, in later years, as successful merchant, banker, public official, he would give all he has.

Keidel<sup>18</sup> in 1931 estimated the cost to the patient of treating syphilis



in Baltimore at minimum private rates as \$380 for a period of 15 months, and the cost at average rates to be \$650.

Bromberg and Davis<sup>5</sup> believed the cost to various patients may be expected to differ because of: 1, Medical factors, particularly the state of the disease at which treatment is begun. 2, Public health provisions, particularly the extent to which health departments provide free serologic tests or arsphenamines. This is done in some localities but not in others. 3, Social and economic factors, such as the financial circumstances of patients, the prevailing scale of medical charges and of prices for drugs, at different times or in different parts of the country.

Because of these varying elements, Bromberg and Davis<sup>5</sup> believed no single amount can be designated as "the" cost of treating the disease. Tentative cost figures are applicable to specific local conditions and to a specified period of time. Based upon the cost of a "standard treatment" for one year, or by ascertaining the cost of treating some actual cases, these authors decided the cost to the patient of the "standard treatment" by a general practitioner, at minimum rates, for a patient not regarded as an object of charity, would be \$268 for one year. The expense at the minimum rate of the specialist would be \$485. The cost to the patient at the rate of the better known specialist would be \$1050. If the patient were treated at a pay clinic, the cost would be, depending on the clinic, about \$133, or \$169 for a grade of service for which \$300 to \$900 more would have to be paid for private care.

For the actual treatment given to 7 patients by private practitioners, \$273 to \$723 was spent, with the expense for 1 individual case reaching a maximum of \$1425. Bromberg and Davis<sup>5</sup> felt that a figure of \$300 could be used as the minimum at private rates for the adequate treatment of syphilis for one year.

Moore<sup>25a</sup> believes that according to estimates, adequate treatment for early syphilis may be furnished at minimum clinic standards at a cost of \$25 per patient; and on the basis of the highest standard of clinic practice, for \$50 per patient. Gehrmann<sup>12a</sup> (1938) also found, after 4 years of operation of a syphilis protective program in the E. I. duPont de Nemours Company, that a complete course of treatment cost the company \$50. Davis<sup>9</sup> estimated (in 1932) that about 80% of the population could not pay for adequate care of syphilis at private rates; about 50% of the population could pay for the adequate care of syphilis at pay clinic rates, although not at private rates; except when the usual minimum fee is cut by the physician to about half; fully one-third of the population, if infected, must receive treatment for syphilis free or for nominal amounts; and the cost of treatment is an important cause of the insufficient or inadequate therapy which many infected persons receive. In this connection Gehrmann<sup>12b</sup> found that "most physicians demand prices for treatment that are beyond the means of the individuals and out of reasonable proportion to their incomes."

Nelson,<sup>29c</sup> in discussing the provision of treatment for genito-infectious diseases in the indigent in Massachusetts, found, after 7 months of experience, that the average cost per clinic visit is approximately \$1. Patients pay about 21% of this cost, and the Commonwealth pays the balance, or about \$200,000 annually. For 79 cents per visit, the

Commonwealth provides not only for the treatment of these clinic patients, but also for reasonably adequate case control and case finding, done by the clinic personnel. Furthermore, the Department approves of the payment of the clinic medical personnel wherever possible, so that for slightly over 75 cents per visit, the Commonwealth purchases full treatment, follow-up, and epidemiologic service for those who are unable to pay for private medical care, and who are able to reach clinics. In order to reach individuals at distances, inaccessible from clinics, the Commonwealth has experimented with providing treatment in private practice. On proper application, the physician is allowed by the Commonwealth \$2 per visit. This fee is over and above any drugs which are supplied free by the Commonwealth to physicians and clinics alike, for the treatment of syphilis. This and similar attempts to compensate private physicians on a fee basis have resulted in such abuse that efforts along these lines have been largely abandoned. No satisfactory substitute applicable to all rural areas has yet been devised, though in some sections the traveling clinic or employment of selected physicians on a salary basis to treat patients in their offices free or at a reduced fee basis has proved more practical than remuneration on a purely basis for treatment-patient visits.

If the 250,000 visits made to clinics were to be paid for at private rates, it would have cost the Commonwealth of Massachusetts \$500,000 annually, instead of \$200,000, and this, more than double cost, would have paid for treatment only. Actually, it has cost the Commonwealth approximately \$20,000 per year to provide treatment at private rates for the relatively few patients who cannot attend the clinics. It costs another \$30,000 annually to provide hospital care for patients who need and cannot pay for it.

Nelson's<sup>29c</sup> estimate of about \$1 for the treatment of syphilis in the various Massachusetts clinics comes close to Keidel's<sup>18</sup> figure of \$1.03 per visit for patients coming to the Johns Hopkins Hospital Clinic in 1931. Goldberg<sup>14b</sup> also found that \$1 per clinic visit was a suitable standard figure for clinic visit costs in New York City.

**Hospital, Clinic, and Laboratory Costs of Syphilis (Direct Costs).** Three methods, according to Brumfield<sup>6</sup> have been followed as a means of obtaining data on the true costs of syphilis. In the first, used by Loeffler<sup>20</sup> in a survey in St. Louis in 1932, an effort was made to determine by questionnaire not only cost of treatment in private practice, but also indirect costs such as relief to families of wage earners incapacitated because of the disease and of legal proceedings involved in the supervision of prostitution. This study did not separate the costs of gonorrhea and syphilis. Brumfield and Goldberg criticized this survey on the grounds that the sample of information obtained from physicians answering the questionnaire cannot be translated to indicate the experience of those who did not reply. They contended that it is impossible to determine the proportion of hospital overhead expense which was allocated to venereal disease patients and the data obtained from agencies concerning indirect costs cannot be relied upon, since the proportion of those costs attributable to the venereal diseases is not definite. Goldberg believed that \$1,000,000 of the total estimated minimum of some \$2,000,000 was open to criticism.

A more reliable study of the direct costs of syphilis was made by

Thompson, Brumfield, and Caldwell.<sup>40</sup> They selected Baltimore in the year 1933 for their study. Their investigation was limited to those items for which they believed reasonably accurate information could be obtained. Data were secured from the actual records of the hospitals and institutions studied, and the survey was restricted to current expenditures, with no effort to estimate fixed overhead or fixed charges on capital investment, so that it included only the costs of hospitalization and clinic facilities, including laboratory services in connection with them and antisypilitic drugs. These investigators found that the total measurable direct expense of syphilis to the city of Baltimore during 1933 was about \$170,000 less about \$11,000, the amount paid by patients. It is important to call attention to the fact that the total figure is the unquestioned minimum cost, and does not include any of the following indirect costs, the proportionate total of which ascribable to syphilis can only be surmised: 1, Fixed overhead of hospitals, clinics or laboratories; 2, fixed charges in capital investment of hospitals; 3, library service for blind syphilitics; 4, special schools for handicapped children; 5, blind pensions; 6, sums expended by private physicians and private laboratories; 7, fees paid by patients to private physicians and laboratories; 8, relief paid by Federal Government or local charitable agencies to patients disabled from syphilis, or to their families; 9, legal and police measures for the repression of prostitution; 10, money wasted by patients with quack physicians and cultists; 11, cost of self-treatment at drug stores; 12, economic losses to industry and society.

Thompson and his co-workers then concluded that: 1, The total *direct* cost of syphilis to the city of Baltimore during 1933 was (roughly) \$170,000; 2, indirect costs were not estimated; 3, in direct community costs alone, each new syphilitic patient was responsible for the charitable expenditure of about \$18 per year; 4, only by a reduction in the incidence of syphilis can the total expenditure be decreased; 5, only by the provision of adequate ambulatory clinics can the incidence of syphilis be reduced.

Goldberg<sup>14b</sup> used a third method of approach in the determination of the direct cost of syphilis and gonorrhea in New York City. This survey was limited to those items included in the Baltimore study, the two diseases being considered separately. Goldberg<sup>14b</sup> analyzed a large number of records of representative hospitals and clinics and estimated the total cost from these. His results were surprisingly similar to those obtained in the city of Baltimore.

Brumfield (1938)<sup>6</sup> compared the results of a survey of the hospital, laboratory, and clinic costs of syphilis in Buffalo, New York (population approximately 573,000) for 1936 with similar costs found in the Baltimore, Md. (population approximately 805,000), study by Thompson, Brumfield, and Caldwell in 1933. The total costs in each of these studies approximated each other (about \$165,000 in Buffalo; about \$179,000 in Baltimore), but the distribution of some of the expenditures varied considerably.

In either city the major cost was borne by public expense, by taxpayers direct, or by privately endowed charitable organizations. The cost of hospitalization of late syphilitics greatly exceeded the cost of clinic and laboratory services. This represents a great economic loss since only a few of the patients so hospitalized could be rehabilitated.

"The cost of treatment of late syphilitics in Buffalo was considerably more than in the city of Baltimore. The difference is believed to be due largely to the greater ease with which patients could obtain hospitalization in Buffalo rather than a greater prevalence of syphilis in that city. The excess cost was represented largely in the greater number of Buffalo residents cared for in New York State hospitals for mental diseases.

"A great saving in public funds could be accomplished in either city through case-finding procedures directed toward the placing of patients under treatment in the early stages of the disease and thus preventing late manifestations. The expenditure of funds for such procedures would undoubtedly be saved many times over."

Moore stated that the cost of hospitalization and of direct relief paid to disabled syphilitics, chiefly the insane, parietic, and the irremedial cardiac, may be conservatively estimated in the country as a whole as somewhere between \$35,000,000 and \$50,000,000 per year. This sum could largely be saved by proper attention to early syphilis.

Based upon a \$25 to \$50 per patient standard of treatment for clinic practice, Moore<sup>25a</sup> estimated the total cost of treating the known 518,000 annual fresh infections so well that incapacitation caused by late syphilis and the expense it causes could be decreased to insignificant proportions, would therefore be between \$12,000,000 and \$25,000,000 per year. He believed that if the more probable figures 1,000,000 patients with fresh infections should be treated each year, an annual cost of between \$25,000,000 and \$50,000,000 would be required. Twenty-five million dollars spent for early syphilis will do more good than a much larger amount spent for late syphilis.

Estimates have been made for various items in the cost of the care for syphilitics. Several of these are: 1, Cost of laboratory procedures for the diagnosis of syphilis; 2, cost of antisymphilitic drugs; 3, cost of epidemiologic control; 4, hospital costs.

1. Keidel<sup>18</sup> found that the actual cost of doing a quantitatively titered Wassermann with an additional flocculation procedure on each sample of blood submitted in a small but reliable laboratory, doing 200 tests per month, was \$1.63 per specimen. If 500 tests per month were run, the estimated cost would be 66 cents. The serologic laboratory at the Johns Hopkins Hospital, doing over 50,000 tests per year, does them at an average total cost of 29 cents each. The Massachusetts Department of Health (Nelson and Crain<sup>30</sup>) doing 200,000 tests annually, can do the serologic tests at 12 cents each. Webb and Sellers<sup>47</sup> found that 46 state and 15 city laboratories performed 2,854,000 tests in 1935. Based on Keidel's lowest cost, this comes to \$828,000 annually. Brumfield,<sup>6</sup> in his comparison of Baltimore and Buffalo costs, noted a per capita expense of \$0.043 for Baltimore and \$0.044 for Buffalo. His study, however, failed to mention the actual cost per test. Gehrman<sup>12b</sup> (1938) stated the cost to the du Pont de Nemours Company for a Kahn test was 20 cents.

2. *The cost of antisymphilitic drugs* is variable, dependent upon the types of drugs, the locality in which the drugs are purchased, and the arrangements with manufacturers, which the various agencies supplying the drugs make. The cost of antisymphilitic drugs in Baltimore was about \$7000 while only about \$2000 were spent in Buffalo. The costs

of antisyphilitic drugs in Baltimore were estimated while in Buffalo figures were supplied by the New York State Department of Health.<sup>40</sup>

3. Ingraham<sup>17</sup> has estimated the cost of epidemiologic control work in clinic practice. The cost for complete service includes expenditures directed toward: 1, Instructing the patient. 2, Obtaining usable information concerning sources of infection and contacts, and bringing these contacts under observation. 3, Correspondence, telephone calls, and home visits involved in keeping the patient coming in regularly for treatment.

These figures are on a yearly basis. The total cost of uncovering 0.36 infected contacts per each newly infected case, and of keeping some 35 per cent of patients under active therapy for a year in Clinic II in New Jersey, amounted to \$11.36 per patient per year. This cost in Clinic I in New Jersey, which presents a relatively lower contact rate (0.23 per infected patient) but a higher case-holding ability (57% success) amounts to \$16.58 per patient per year. In the University of Pennsylvania Syphilis Clinic, the cost was \$5.99 for successful follow-up service, and for successful contact tracing, it is \$5.22 per patient. The total cost per patient is \$11.21. This is about equal to the figure for Clinic II in New Jersey.

4. The cost for the hospitalization of syphilitics has also been estimated. This cost for late syphilis is more than the costs of clinic and laboratory services. In Buffalo<sup>6</sup> this item represented about two-thirds of the total expenditures. In Baltimore it was less than half of the total outlay. Goldberg<sup>14b</sup> found that the New York City hospitals and the State hospitals admitting patients from the city were obliged to expend more than \$1,000,000.

**Estimated Cost of Maintaining a Program for the Control of Gonorrhea and Syphilis.** The Advisory Committee to the United States Public Health Service<sup>1</sup> in 1935 prescribed a program for the control of gonorrhea and syphilis by state and local health departments. The cost of carrying out these recommendations has been estimated for Massachusetts by Nelson.<sup>29a</sup> It would require a budget about twice as large as the budget in force in 1935 for the essential program and one about four times as large for the recommended program.

Nelson<sup>29a</sup> believed that if total appropriations from all public funds for the control of communicable diseases are taken into consideration, that part spent for the control of gonorrhea and syphilis must be relatively insignificant. On that basis, the expenditure by the state of between \$300,000 and \$400,000 annually cannot be considered as a disproportionately large sum for the control of two such prevalent and economically serious diseases as syphilis and gonorrhea. He further stated "that large sums of money have been appropriated for the control of tuberculosis, for the purification and protection of water supply, and for the control of cancer because the public has learned that these things are worth spending money for. The need should determine the expenditure rather than relative prevalence. Nothing could be more striking than the \$1,272,580 spent by the State for the control of tuberculosis (in 1935) compared with \$259,425 spent for the control of other communicable diseases, whereas the reported prevalence of tuberculosis is only 5.1 % of the reported prevalence of all communicable

diseases. On the basis of relative prevalence, only \$13,000 should be spent on tuberculosis."

The Massachusetts Department of Public Health spends 6.2 cents per capita exclusive of Social Security funds on syphilis. If the same per capita rate were expended by all of the State Departments of Health, the total outlay would only be about \$8,000,000 in this country of an estimated 130,000,000 population. This sum is small in comparison with the \$50,000,000 needed for the adequate care at clinic rates of only those fresh infections which come to medical attention annually.

It may be pertinent to comment here briefly on the question of the reaction of many physicians to the state and national program, based upon fears of socialization of medicine. While it is definitely not appropriate to make polemic issue of this problem here, the analysis by Gilman<sup>13</sup> of the competition of the State with private practice reduces the arguments to absurdity. For example, he calculated, on the basis of \$3,000,000, appropriation for the whole of the United States set aside for syphilis control for 1938 that a sum of 80 cents per year per clinic patient was available. This figure is based on the assumption that all of the money is expended in syphilis control.

**Costs, Direct and Indirect, for Various Aspects of the Syphilis Problem.** *Cost of Syphilis to Industry and Labor.* In the review of Syphilis in Industry by Stokes, Beerman, and Ingraham<sup>39</sup> it was pointed out that figures for the cure of syphilis in industry have still a somewhat speculative character. Many of them are old and possibly outdated; based on individual surveys of industries whose identities are concealed and whose representative character for the problem in general or the country at large cannot be determined. Among the most quoted estimates are those of Parker<sup>31</sup> (1932), including 12% syphilis in a group of railway employees exhibiting delayed convalescence and disability whose total loss of time represented 13,946 days, and \$48,711. A large industrial concern, unnamed, whose personnel efficiency had dropped below expectations, found that 1 in 10 employees had gonorrhea or syphilis, 68% of the non-effective employees were on the sick list because of these diseases, and those venereally diseased had lost three times as much time as persons not affected. Each person with syphilis or gonorrhea was paying out an average of \$75 a year for such treatment as was being given. The establishment of a clinic within the industry for adequate treatment and assistance to these persons presently offset the cost to the establishment by increased production. A West Virginia manufacturing concern, as a result of the installation of a clinic for venereal disease costing \$5000 to \$6000 for the first year, sustained an increased efficiency of 35%.

"It is clear from a review of the literature that statistics providing adequate differentiation among types of employees, types of industry, and obtained by methods other than mere routine serologic testing of blood, are really needed before the problem can be envisaged in its entirety, and principles formulated."

Among the general male population, aged 15 to 45, the number of days lost from work through venereal diseases is at least equal to 21,000,000 per year. At the average wage of \$4 per day, \$84,000,000

in wages are lost, to say nothing of the cost to employers, compensation, medical costs, and labor turnover.<sup>2</sup>

Moore<sup>25b</sup> has made a thorough discussion of the problems, social and economic, involved in syphilis and unemployment. He has not, however, estimated the possible financial cost of this important subject.

*Syphilis and Crime.* Without entering into a discussion of the social implications involved in the problem of syphilis and crime, it is interesting, even if not more than coincidental, that among prisoners the incidence of syphilis is higher than in non-criminal groups. This whole subject was discussed by Church<sup>7</sup> in 1938.

Parran's Committee<sup>15,16,19,22,28,36,37,41-43</sup> reported from the literature, among 119,000 individuals which represents the average prison population for Federal and State prisons in the United States, there were on an average of from 160 to 170 per 1000 individuals with positive blood tests for syphilis.

Surgeon Hawk<sup>15</sup> of the United States Public Health Service found in the prisoners of the penitentiary at Fort Leavenworth, that the prevalence was highest among negroes, 36.4 %; 34.9 % for the red-brown races; 19.1 % for the Caucasian race; and 11.4 % for the Mongolian race, with a general average prevalence of 21.7 % for a period of 2½ years. Keil<sup>19</sup> found 18.2 % positive blood tests in an Ohio penitentiary. Heller<sup>16</sup> (1936) in a study of the short-term prisoners in a penitentiary, in eastern Tennessee, found positive blood tests for syphilis in 20.2 % of the whites and 44.6 % of the negroes with an average percentage of 29.3 %. As a control for the incidence among these two groups, Heller used statistics on negro families in rural Tennessee, among whom 26 % had positive blood tests, while a white survey in an industrial plant in the same section of the State yielded 4.1 % positive tests. Negro males in an industrial project yielded 15 % positive tests. Heller also found that 30.2 % positive serologic tests in the spinal fluid in the whites; 21.1 % in the negroes, and an average of 24.6 % in both. He felt that the actual percentage may be higher since only patients with positive blood tests had their spinal fluids examined. Of those with neurosyphilis, 45 % showed enough positive signs to make the diagnosis clinically. Church<sup>7</sup> also cited a number of statistics regarding the association of syphilis and homicide.

It is obvious, although syphilis is not blamed for criminality, from the frequency of syphilis among criminals that this disease cost the community a considerable amount of money. The exact sum is by no means calculable.

*Syphilis and Insurance.* The problem of insurance and syphilis is receiving increasing attention. There are no accurate statistics on the number of individuals who sustain insurance benefits or economic losses in the form of increased premiums because of syphilis. Compensation paid because of the contributory effects of syphilis is likewise an indefinite quantity. The detection of syphilis in applicants for insurance can be facilitated by the use of a sensitive precipitation test as suggested by Rein, LeMoine, and Stephens.<sup>33</sup> Murrell and Manson<sup>37</sup> and Short and Kelley<sup>35</sup> in recent papers made observations on the incidence of syphilis among insurance applicants and suggestions for the equitable solution of this problem.

*Cost of Quack Medicine and Self-prescribing.* This phase of the cost of syphilis is again one which defies estimation. It is, however, recognized that it represents a large figure and in the careful study of Edwards and Kinsie<sup>11</sup> there is some indication "that the sale of such patent remedies is now even greater in volume than 6 to 8 years ago." They further found that large numbers of charlatans, herbalists, and other unlicensed practitioners are treating many persons having syphilis and gonorrhea.

*Syphilis and Death.* This item of cost of syphilis is difficult to estimate. Not only are the deaths directly attributed to syphilis not reported by physicians, but many are actually unrecognized. In addition, the cost of premature deaths is an item which must be taken into account. Usilton<sup>44b</sup> determined that life expectancy of males with syphilis is shortened from that in the general population from 30 to 60 by 17% in the white males and 30% in the negro males. The preliminary Mortality Summary for Large Cities (1939)<sup>26</sup> showed a rate of deaths from syphilis of 9.8 (1936) per 100,000 population; 10.2 per 100,000 population in 1937; and 9.7 per 100,000 population in 1938.

On the basis of extensive literature Parran and his Committee<sup>32</sup> from the United States Public Health Service estimated that approximately 40,000 deaths from cardiovascular syphilis occur every year in the United States, at least 6.5% of which are syphilitic in origin. Since each death represents a loss of from 19 to 23 years of life, it is estimated the total loss of life from cardiovascular syphilis is around 800,000 to 850,000 years annually. Deaths from paresis represent a loss of about 100,000 years annually.

*Cost and Loss From Syphilis Blindness.* This subject has been admirably summarized by Surgeon C. E. Rice<sup>34</sup> of the United States Public Health Service. After a preliminary survey of the various factors involved in the incidence and cost of this phase of syphilis, Rice<sup>34</sup> found that syphilitic blindness costs the United States about \$10,000,000 in the loss of earnings and in costs of supporting these blind individuals.

Syphilis accounts for about an average of 15% of the blindness. Rice has cited estimates ranging close to this average figure, which he used as the basis for his calculations. While this average percentage is generally acceptable, it is worth noting that recent authorization studies based on fairly large series of cases have given relatively lower figures (Berens, Kerby, and McKay,<sup>4</sup> 5.3%; Berens and Goldberg,<sup>3</sup> 6%; Cowan and Sinclair,<sup>8</sup> 9.4% among applicants for pensions for the blind in Pennsylvania; Long and Goldberg<sup>21</sup> cite: 0.45% interstitial keratitis in eye cases in Boston; National Society for the Prevention of Blindness, 15% of the blindness due to syphilis among about 5000 applications for pensions for the blind, University of California Dispensary, 9.5%). Even if 15% is considered a little high as the average incidence of syphilitic blindness, Rice's<sup>34</sup> figures are so conservative that the minimum cost of about \$10,000,000 is unquestionable.

The statistics, roughly estimated, for the State of Pennsylvania, have been given to me in a personal communication by Miss E. M. Carpenter, of the Philadelphia Committee for the Prevention of Blindness, Inc. Eighteen per cent of a total of 27,000 applicants for blind pensions have syphilis (13,000 were granted pensions). The average cost



per year per person as a pensioner is \$360. It is estimated that it costs \$10,500 to educate one blind child through twelve grades. There are about 500 children in two schools for the blind in Pennsylvania. One-third of these children are presumed to be syphilitic. The cost for this education is supplied by the State (75%) and local philanthropies (25%).

*Costs of Cardiovascular Syphilis.* Ten to 18 per cent of the load of cardiovascular clinics has been estimated as due to syphilis. It is obvious that a specific estimate of the total cost, both direct and indirect, of this large amount of disability due to syphilis can hardly be accurately estimated. However, certain parts of the costs can be approximated. For example, Brumfield<sup>6</sup> showed that the hospital costs in Baltimore for cardiovascular syphilis was about \$11,000 whereas for Buffalo the cost for hospitalization was about \$8000. It is pertinent to realize that the expenditure for hospital care for cardiovascular syphilis is apparently a lighter burden than that for neurosyphilis, but this must not be interpreted to indicate that cardiovascular syphilis is relatively unimportant, since it results in death relatively soon, or the patient may be rehabilitated to the extent that he can be cared for at home, even though he might be unable to return to gainful employment. The result is that the economic losses from this manifestation will be represented largely in indirect costs.

*Neurosyphilis.* The incidence of neurosyphilis is one of the major factors in mental disease. Merriman<sup>24</sup> (1935) estimated that neurosyphilis occasioned 11.3% of all admissions to civil state hospitals during the year ending 1933, and he restated the estimate that neurosyphilis cost the State of New York alone \$13,500,000 during the year 1931. Malcolm H. Merrill,<sup>23</sup> Chief of the Bureau of Venereal Diseases of the State of California, estimated that this State is forced to spend approximately \$250,000 a year for the care of the syphilitic insane who are only one small group of those who are dependent because their syphilis was undiscovered or untreated. An editorial, commenting on "Dangerous People At Large,"<sup>10</sup> pointed out that the hospital facilities used "by our parietic company will represent an investment of over \$1,250,000." Brumfield<sup>6</sup> found the hospital costs for neurosyphilis in Baltimore and Buffalo to be the greatest expense in either city. In Baltimore, this item cost about \$51,000, whereas in Buffalo the cost of hospitalization was about \$95,000.

In addition to the economic losses and the cost for hospitalization, as well as other indirect costs of neurosyphilis, paresis and tabes are a factor in the death rate from syphilis. Fortunately, this cost appears to be decreasing.<sup>33</sup>

As was stated in the beginning of this survey, one cannot estimate with any degree of exactness the actual cost of syphilis. The reliability of the data given is questionable, regardless of how carefully they were compiled. One thing is certain. The cost of syphilis is enormous, even in these days when millions or billions of dollars are spent by governments daily. Treatment for syphilis will wholly prevent this unnecessary expense. It is obvious that untreated syphilis is a luxury for any individual or community.

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## PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1940

Simultaneous Renal and Hepatic Excretion of Water and Various Dyes in Rabbits. WILLIAM E. EHRLICH (Department of Pathology, School of Medicine, University of Pennsylvania). The excretion of water,

cyanol and azofuehsin I were studied simultaneously in simple bile drainage experiments and in those in which urea was given to stimulate diuresis. In addition, experiments were performed in which either the common bile duct or the renal arteries and veins were ligated. Ligation of the common bile duct did not as a rule influence diuresis, and administration of urea did not influence the bile rate, while ligation of the renal arteries and veins was followed by a drop in the rate of bile excretion. The renal excretion of the dyes depended chiefly on the urine rate in all experiments, more dye being excreted with better diuresis and *vice versa*. The hepatic excretion of the dyes on the other hand was not merely a function of the bile rate, but depended on both the bile rate and the urine rate (*i. e.*, the renal elimination of the dyes). The faster the bile rate and the slower the renal elimination of the dyes, the greater the amount of dye that was excreted in the bile.

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**The Biologic Activity of Some Cortin-like Compounds.** DWIGHT J. INGLE (George S. Cox Medical Research Institute, University of Pennsylvania). Desoxy-corticosterone is the most active of the known steroid compounds in its life-maintaining capacity. The compound 17-oxy-11-dehydro-corticosterone has little or no life maintenance effect. The earlier observation has been confirmed that 17-hydroxy-11-dehydro-corticosterone has an apparently greater effect upon the work performance of adrenalectomized rats than does desoxy-corticosterone when the first 24 hours following operation are used as a test period.

In addition, adrenalectomized male rats having an initial body weight of 180 gm. were treated for 1 week with these two compounds and at the end of this period their work capacity was studied. The rats treated with desoxy-corticosterone gained in weight even when the doses were small, and although their capacity to work was improved over that of untreated animals, their performance was poor even when as much as 10 mg. was administered daily. All of the animals treated with 17-hydroxy-11-dehydro-corticosterone lost weight to the same extent as untreated animals, but their work performance was improved above that of the animals treated with desoxy-corticosterone. Similar animals treated with a mixture of desoxy-corticosterone and 17-hydroxy-11-dehydro-corticosterone performed more work than animals treated with an equal quantity of the single substances.

Although the results may be due to changes in the efficiency of utilization of these compounds when they are administered in different test situations, the findings are also in harmony with the hypothesis that there are qualitative differences in the biologic effects of some of the cortin-like compounds.

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**The Effect of Temperature and of Starvation Upon Growth of Frog Carcinoma.** BALDUIN LUCKÉ and HANS SCHLUMBERGER (Laboratory of Pathology, School of Medicine, University of Pennsylvania). For studying the effect of temperature on growth of tumors, the kidney carcinoma of the leopard frog, *Rana pipiens*, is particularly good material, as this tumor grows well when inoculated into the anterior chamber of the eye where it may be kept under continued observation (*J. Exp. Med.*, 70, 251, 1939); and as it is able to establish itself and increase in size at temperature differences of at least 20° C.

In the first series of experiments, frogs, immediately after being inoculated, were transferred to a constant temperature room, at  $7^{\circ}$  C., control groups being kept in the vivarium at  $22^{\circ}$  C. They were observed for 2 to 6 months, and during this time they received no food, as frogs at the lower temperature will not eat. It was found that the tumors were able to establish themselves and grow at both temperatures, though the proportion of takes was slightly less at  $7^{\circ}$  than at  $22^{\circ}$ . Massive tumors, however, developed only at  $22^{\circ}$ ; this fact seems to be due to more effective vascularization at the higher temperature. When the frogs with large, well-vascularized tumors were transferred from the vivarium to the cold room, growth of tumors continued, but at a slower rate.

In the second series of experiments, the effect of temperature was studied on tumors that had already become established. Following inoculation in the anterior chamber, frogs were kept in the vivarium for 2 or 3 weeks, or until the transplants showed evidence of beginning growth. The frogs were then transferred to constant temperature rooms, at  $7^{\circ}$  C. and at  $28^{\circ}$ , respectively. It was found that the rate of growth was greater at the higher temperature, though there was little difference in the size which was finally attained. Regression of the tumors developed in a higher percentage at  $28^{\circ}$  than at the lower temperature.

In a final group of experiments, the combined effects of extreme starvation and low temperature was investigated. Markedly emaciated frogs which had been kept at  $7^{\circ}$  for several months were inoculated and then returned to the cold room; as controls, well-nourished frogs with intraocular transplants were maintained at  $28^{\circ}$ . It was found that even in the starved animals, cold did not prevent growth of transplants, though growth was less vigorous than in the control group.

The general conclusion to be drawn from these experiments is that low temperature,  $7^{\circ}$  C., does not arrest nor change the mode of growth of frog carcinoma transplanted to the anterior chamber; it does, however, reduce the velocity of growth, possibly by preventing early vascularization. High temperature,  $28^{\circ}$  C., while increasing velocity of growth, also tends to lead to its earlier decline and to retrogression of the tumors.

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**Surgical Correction of Hypomenorrhea and Hypermenorrhea by Isoplastic Grafts.** MICHAEL JOHN BENNETT (Broad Street Hospital). The ovarian isoplast is produced by an abdominal operation which interchanges a portion of one ovary from each of 2 patients. Fifty such grafts have been made in this hospital since February, 1935. The patients are carefully selected after 2 to 24 months of preliminary study in which it is established that one of each pair possesses ovaries of the hyperinterstitial, the other of the hypointerstitial, type.

At the time of operation, the hypointerstitial and hyperinterstitial ovaries are simultaneously resected at the hilus without hemostasis. The resected tissue is immediately transferred from one hilus to the other. The peritoneal coat of the stump and the peritoneal coat of the transported ovary are coapted by means of a continuous suture of No. 00 chromic catgut on an atraumatic needle. No complications have followed.

Following these operations an improvement in ovarian rhythm, appearance of vaginal smears, esterone and prolactin concentrations, and chemical constituents of the blood have been noted and no patient has required a continuation of hormonal medication. We believe that ovarian isoplasty tends to stabilize metabolic imbalance caused by ovarian dysfunction and that such grafts will grow with a normal nerve and blood supply if they are made in the manner described and in carefully selected patients.

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ORIGINAL ARTICLES.

STUDIES ON "ESSENTIAL" HYPERTENSION.  
III. THE EFFECT OF NEPHRECTOMY UPON HYPERTENSION  
ASSOCIATED WITH ORGANIC RENAL DISEASE.

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ARTERIAL hypertension is found in patients whose kidneys exhibit a variety of lesions and who suffer from renal insufficiency. Similar lesions have been found in hypertensive patients who are free from renal insufficiency.<sup>5,12a,b</sup> That these lesions play a part in the existence of hypertension is shown by the fall in blood pressure which has been reported to follow removal of a single affected kidney. Butler was the first to record this result in 2 children suffering from pyelonephritis.<sup>4</sup> Similar occurrences have been observed both in children and adults (Table 1). Of the 12 reported, 7 cases were improved. Only 3 were observed for more than a year and all were years and remained free from hypertension for 10; finally, however, it recurred.\* The other cases were published before an adequate interval had elapsed. The late results of nephrectomy in adults are therefore uncertain, although in every instance the immediate effect was a lowering of blood pressure for a matter of months. The inference that can be drawn from all the information now available

\* A review of the older urologic literature has failed to reveal the effect of nephrectomy upon the arterial pressure, or of cases similar to those which have recently been published. Barney and Suby,<sup>2</sup> however, mention a series of 305 cases of pyelonephritis and hydronephrosis in the records of the Massachusetts General Hospital, of which 25% exhibited hypertension. It is hoped that other similar statistics will soon be available in the literature.

constitutes, accordingly, an unsatisfactory basis for drawing a conclusion on the value of this operative procedure; for the most part the cases were in young persons; the duration of observation was short; the end results are uncertain. The effects of operation observed in the period of weeks or months afterwards make desirable a further analysis of cases so treated. To follow out this plan is

TABLE 1.—SUMMARY OF CASES PREVIOUSLY REPORTED IN THE LITERATURE.

Reported by	Age. Sex.	Pre-operative range of B. P.	Post-operative range of B. P.	No of mos. followed.	Maximl urine concentration, specific gravity.	Phenol-phthalein excretion 2 hrs. (%)	Renal lesions.	Result.	Remarks.
Butler <sup>4</sup>	7 ♂	168/110 122/90	115/75 100/70	20	1.024	55	Pyelonephritis	Improved	Moderate arteriolar sclerosis of kidney
	10 ♀	190/120	110/70 92/60	3	..	Normal	Pyelonephritis; dilated pelvis	Improved	Marked arteriolar sclerosis of kidney
Pincoffs and Bradley <sup>11</sup>	2 ♀	180/110+ 150/110	130/100	3	1.032	80	Adenosarcoma	Slight improvement	Patient died of recurrence. B. P. rose to former level
	2 ♂	140/100 120/80	88/60	7	1.028	80	Adenosarcoma	Temporary improvement	B. P. normal for 6 mos., but returned to previous level
Barker and Walters <sup>1</sup>	42 ♂	200/140 170/120	144/100 128/90	2	..	Blood urea normal	Atrophic pyelonephritis	Improved	Thickened arcuate and interlobar arteries. Scarring of kidneys
Leadbetter and Burkland <sup>3</sup>	5½ ♂	174/120 132/82	120/74 96/70	1(?)	1.026	90	Ectopic kidney; partial occlusion renal artery by plug of smooth muscle	Improved	No intrarenal vascular disease
Boyd and Lewis <sup>3</sup>	31 ♂	225/140 165/100	150/100 125/75	6	1.017	70	Infarction of kidney	Improved	Narrowing of renal arteries
Quinby <sup>8</sup>	14 ♂	250/170	130/7	12+	1.015	15	Hydronephrosis; chronic pyelonephritis	Temporary improvement	Marked destruction of kidney
Crabtree <sup>5</sup>	27 ♀	210/? 180/?	190/? 120/76	134	..	45	Chronic pyelonephritis; stricture of ureter	Improved 10 yrs.	Return of hypertension 11th year
	40 ♂	170/120 100/72	120/88 100/70	2	1.028	50	Calculi; pyelonephritis	Improved	Narrowing of intrarenal arteries
Barney and Sibly <sup>2</sup>	10 ♀	200/170 185/130	110/70 98/60	21	..	61	Pyelonephritis with atrophy	Improved	Marked renal vascular disease
McIntyre <sup>9</sup>	35 ♂	180/104 168/94	150/94 128/78	9	1.024	35	Pyelonephritis; double kidney; hydronephrosis	Improved	Narrowing of main renal artery by arteriosclerosis

\* Reported by Crabtree.<sup>5</sup>

reasonable because renal affections have been found to be so common in cases of arterial hypertension. Nephrectomy has therefore been performed in 7 instances. Two patients were not improved and have subsequently died; 2 were improved for some time (16 and 11 months); 1 was temporarily improved; and in 2, no change has been observed. In no instance has hypertension disappeared. These 7 cases will be discussed separately.

Patients were selected in whom severe arterial hypertension was

associated with unilateral renal disease accompanied by marked diminution of function of the affected kidney but not by renal insufficiency. In 4 there was evidence of disease of the opposite kidney of lesser degree, and in 3 no other lesion was demonstrated. It must be emphasized that little difficulty was encountered in finding such cases; they are common among younger individuals.

**Case Reports.** CASE 1.—(Hosp. No. 10,354). H. S., aged 35, was a taxi driver who had suffered from arterial hypertension for 2 years. His mother died of high blood pressure at the age of 67. In 1926 he experienced an attack of renal colic and hematuria from which he rapidly recovered. There were 2 similar attacks during the next 2 years. His blood pressure was normal in July, 1936, but in March, 1937, his systolic pressure was 190 mm. Hg.

In December, 1937, examination revealed the presence of a small hemorrhage at the temporal side of the left optic disk. The vessels of the retina were narrow and slightly tortuous with obvious irregular areas of constriction. The heart was enlarged in Roentgen ray photographs; there was diffuse thickening of the radial arteries. His systolic pressure was 210, his diastolic 130 mm. Hg. The urine showed a trace of albumin with many white cells, singly and in clumps. The clearance of urea\* was 84% of normal. Shortly after this he suffered an attack of pain in his left costo-vertebral angle; urination was painful. A small amount of hydronephrosis existed on the right (pyelogram after intravenous injection†) and in the left renal pelvis was a large, rounded, apparently movable stone. In February, 1938, reexamination of the ocular fundi showed a small fresh hemorrhage near the right optic disk and a scar on the temporal side of the left one. Cystoscopic examination was performed and separate specimens from the two kidneys showed that the clearance of urea on the right was 37.7% of normal; on the left, 22.6%. Maximal specific gravity of the urine‡ was 1.022; there were very many white blood cells, single and in clumps, and culture showed the presence of *Escherichia coli*. He was transferred to the Squier Urological Clinic for operation which was performed March 7th. The left kidney was found to be granular and smaller than normal, and its capsule was thick, fibrous and densely adherent. The stone was found fixed in the ureter, which was dilated above it, and there was an artery crossing the uretero-pelvic junction, producing angulation. The stone was removed and nephropexy done. Because of infection in the wound and the development of a huge hydronephrosis and hydro-ureter on the left side, nephrectomy was later performed. Following discharge he developed an attack of acute pulmonary edema, from which he rapidly recovered. In June, 1938, cultures of the urine again demonstrated the presence of *E. coli*, and no change in his blood pressure had occurred. A considerable amount of pus was found in his urine which did not disappear on treatment.

In August, 1938, he was readmitted because of several attacks of paroxysmal nocturnal dyspnea. Bilateral papilledema of two diopters with perivasculitis was seen in the ocular fundi, and there were many flame-shaped and linear hemorrhages with areas of exudate and scars. The urinary infection persisted in spite of therapy with sulfanilamide.

The symptoms of heart failure increased, his clearance of urea fell, and

\* By "clearance of urea" is meant that of Van Slyke.

† By "pyelograms after intravenous injection" is meant Roentgen ray photographs of the genito-urinary tract after the intravenous injection of Diodrast.

‡ By "maximal specific gravity of the urine" is meant the non-protein specific gravity after rigid restriction of fluids for 36 hours.



his blood urea nitrogen became elevated. He died on December 2, 1938, of cardiac and renal failure.

*Description of Specimen.* The left kidney measured 9 by 4 by 2.5 cm. The capsule was thickened, shaggy, and densely adherent to the parenchyma. The renal substance measured 1 cm. in thickness and was opaque and gray in appearance. There was marked dilatation of the pelvis and calyces. On microscopic section many areas of extensive fibrosis were seen through which there was infiltration with lymphocytes. Many glomeruli were fibrotic; in others Bowman's capsule was thickened and adherent to the glomerular loops. The tubules were dilated and atrophied and contained purulent casts and calcareous debris. There was marked thickening of the intima and media of the smaller arteries and arterioles, some being totally occluded.

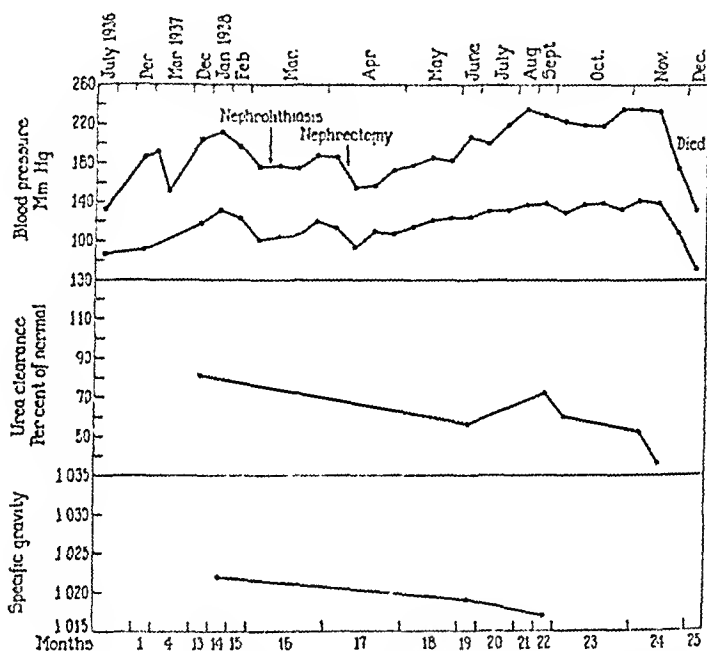


CHART 1.—Showing course of Case 1. Upper line is average systolic; lower, average diastolic pressure. The urea clearance refers to that of Van Slyke. Specific gravity refers to the maximal specific gravity of the urine after fluids were restricted for 36 hours. Months refers to duration of arterial hypertension.

*Autopsy: Right Kidney.* The kidney weighed 265 gm. The cortex appeared hypertrophied, and the calyces stood out distinctly and were slightly dilated, as was the lower ureter. On microscopic section, the tubules were seen to be markedly dilated, extending to the surfaces of the cortex in many instances. The glomeruli were decreased in number and appeared to be arranged in groups radially from the calyces instead of being scattered irregularly throughout the cortex as is found in the normal kidney. In these radial areas there was usually a great deal of fibrosis and between them were dilated tubules. The glomeruli themselves were thickened and Bowman's capsule was distended. There was no congestion in the kidney, but the vessels, particularly the arteries, showed a thickened medial wall.

*Anatomic Diagnosis.* Pulmonary infarction; marked hypertrophy of heart; chronic passive congestion of liver; diffuse arteriolar sclerosis; arteriolonephrosclerosis, mild; cyst of pars intermedia of pituitary gland.

*Comment on Case 1.* Arterial hypertension exhibiting a "malignant" course was associated with bilateral organic renal disease. There was a calculus in the left kidney, hydronephrosis, aberrant renal artery constricting the ureteropelvic junction, and pyelonephritis. There was also right hydronephrosis of slight degree with infection. Removal of the left kidney resulted in no change in the rapid, downhill course. Death occurred from cardiac and renal failure. There was marked vascular disease in the kidney removed at operation, but it was minimal in the remaining kidney. In addition, a cyst of the pituitary was found.

CASE 2.—(Hosp. No. 10,598). A similar event occurred in the case of B. W., a 30-year-old housewife, who had suffered from hypertension for 8 years. Her mother died of hypertension and her father's sister exhibits it. At the age of 8 she became ill for several months because of "pus in her kidneys." Pyuria, low grade fever, and loss of weight occurred. She continued to show pus in her urine on occasional examinations for the next 12 years, but was aware of no other symptoms. Her blood pressure was normal at the age of 21, when she was married. She was soon pregnant. In the sixth month her ankles became swollen, she suffered severe headaches and her blood pressure was found to be elevated. Nausea, vomiting, headache, edema, Pal's crises, hypertension and albuminuria made termination of the pregnancy necessary and a live infant was delivered. Her blood pressure did not return to normal. At age 29 her systolic pressure varied from 260 to 210, her diastolic from 150 to 120 mm. Hg. Her heart was only slightly enlarged in Roentgen ray photographs. One scar was seen in the retina and the arteries were tortuous. *E. coli* was found on culture of the urine.

Pyelograms after intravenous injection disclosed ptosis of the right kidney with slight dilatation of the renal pelvis. The shadow of the left kidney was small. Cystoscopic examination with retrograde pyelography showed a markedly contracted left kidney with a dilated renal pelvis and upper ureter. Studies of the functions of the two kidneys were as follows:

	Right.	Left.
Phenol red excretion (20 min.) . . . . .	5.8%	0
Clearance of urea . . . . .	24%	4%
Albumin . . . . .	0	+

She was transferred to the Squier Urological Clinic where cultures of the urine from the *right* ureter showed the presence of Gram-negative bacillus of the colon group, while that from the left was sterile. Her systolic pressure varied from 270 to 230 mm. and her diastolic from 170 to 132. The left kidney was removed Dec. 2, 1938. It was very small (12 gm.) and was markedly adherent to the surrounding fatty tissue. The pelvis was dilated, thin, and friable, the ureter small.

Immediately following operation her blood pressure fell temporarily to a level between 180 and 140 mm. systolic and 120 and 110 diastolic, but 3 weeks later it was 240 to 200 systolic and 160 to 110 diastolic, and 2 months after operation it remained at the preoperative level. The clearance of urea had fallen to 41% and exudate, hyperemia of the optic disks, and slight papilledema were noted in the ocular fundi. Cultures of the urine again demonstrated the presence of *E. coli*. She died May 15 of renal failure.

*Description of Specimen.* The kidney weighed 12 gm. The pelvis was dilated and very thin. There were many dense, radial scars of fibrous

tissue extending from the medulla to the capsule, and the cortex was thin. Microscopic section showed dense fibrosis of the parenchyma. There was marked thickening of the intima and media of all the vessels, and in many instances their lumina were obliterated. In a few of the tubules purulent material was seen.

*Autopsy: Right Kidney.* The kidney weighed 200 gm. On section, no cortex was evident, and calyces in five places extended directly to the capsule. The renal parenchyma appeared to be made up entirely of medulla interspersed with fibrous tissue. The calyces, pelvis, and ureter were dilated. On microscopic section, the normal architecture of the kidney was drastically altered. The glomeruli were reduced in number, many being atrophic and some calcified. The normal line of demarcation between medulla and cortex was destroyed and many groups of glomeruli were definitely in the medullary area. There was extensive irregular dilatation of the tubules with many areas of degeneration, some being infiltrated with numerous round cells and fibroblasts. Almost all of the arteries and arterioles showed marked thickening and sclerosis of the media.

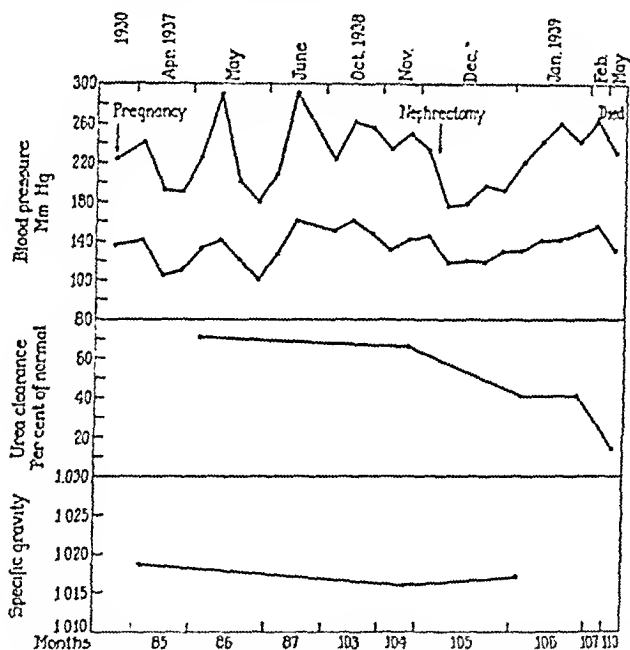


CHART 2.—Showing course of Case 2. Notations same as Chart 2. Blood pressure was said to have been normal previous to point marked "pregnancy."

*Comment on Case 2.* Infection of the kidney in childhood apparently became chronic. Pregnancy resulted in toxemia with hypertension. The left kidney was found to be contracted, and function impaired. Removal of this kidney failed to change the course of hypertension, and death occurred from renal failure 5 months later. There was advanced arteriolar sclerosis of both kidneys. Pyelonephritis associated with hydro-ureter and slight hydronephrosis were present in the functioning kidney.

CASE 3.—(Hosp. No. 10,237). A. L., aged 30, was a stenographer. Her father suffered from hypertension and his brother died as a consequence of it. At the age of 20 she experienced a number of attacks of pain in her

left lumbar region associated with nausea, vomiting, and hematuria. A moderate degree of hydronephrosis was found on the left, with angulation of the ureter at the uretero-pelvic junction and some diminution of function. Her blood pressure was first found slightly elevated at age 24; at 26 was definitely so.

In June, 1937, she complained of severe headaches, moderate dyspnea on exertion, and palpitation. Her heart was slightly enlarged in Roentgen ray photographs. The clearance of urea was 97% of normal. In September, a scar was seen in the ocular fundus and there was evidence of perivascularitis. In February, 1938, pyelograms after intravenous injection showed moderate hydronephrosis on the right with ptosis of the kidney and angulation of the ureter at the uretero-pelvic junction; the outline of the left renal pelvis

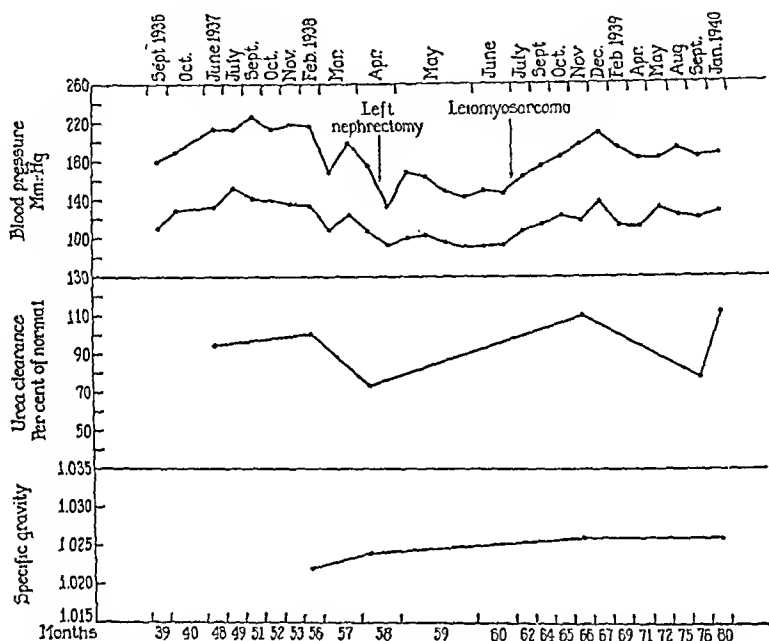


CHART 3.—Showing course of Case 3. Notations same as in Chart 1. At the point marked "leiomyosarcoma" a tumor was removed from the stomach. For fuller explanation see case report.

was not seen. Cystoscopic examination with retrograde pyelography demonstrated a large hydronephrotic kidney on the left, with sharp angulation at the uretero-pelvic junction. The average clearance of urea on the right was 89% of normal; on the left, 21%. Albumin was present in the urine from the right but not in that from the left kidney. She was transferred to the Squier Urological Clinic where left nephrectomy was performed March 14. The kidney was enlarged and the cortex was thin. There were several anomalous vessels about the hilum, and the ureter was kinked about one of these which entered the lower pole. Her blood pressure the day of operation was 270 systolic and 150 diastolic, but on the following day it had fallen to 130 systolic and 90 diastolic, and during her convalescence varied from 120 to 176 systolic and from 80 to 108 mm. Hg. diastolic. In May, 1938, she became anemic and the presence of blood was discovered in the stools. Roentgen ray photographs of the gastro-intestinal tract revealed a large, round defect on the lesser curvature of the stomach. Exploratory laparotomy was performed June 13 at the New York Hospital by Dr. Ralph Bowers, and a portion of the stomach containing a mass was

resected. The tumor was a leiomyosarcoma, but there appeared to be no involvement of adjacent lymph nodes. Convalescence from this operation was uneventful. Her blood pressure before operation was 160 systolic and 100 diastolic, but immediately afterwards and during her postoperative course rose to 180 systolic and 110 diastolic, and 6 weeks later was 162 systolic and 106 mm. Hg. diastolic. In November, 1938, her systolic pressure varied from 200 to 184 and her diastolic from 120 to 110. Since then her blood pressure has remained at this level. There have been no symptoms suggesting recurrence of the neoplasm of the stomach, and she has noticed a complete disappearance of her headaches.

*Anatomic Diagnosis of Kidney.* Hydronephrosis; chronic pyonephrosis; fibrosis and atrophy of kidney; arteriolar sclerosis, moderately severe.

*Comment on Case 3.* Arterial hypertension was associated with bilateral hydronephrosis and right nephroptosis. The left kidney was markedly damaged. Nephrectomy resulted in a sustained fall in blood pressure, which did not reach normal levels and which has approached the preoperative range. The removal of a sarcoma of the stomach did not lower the level of the blood pressure. There was symptomatic improvement following nephrectomy. A moderately severe grade of vascular disease was found in the affected kidney.

CASE 4.—(Hosp. No. 8947). M. B., was a nurse, aged 33. A maternal aunt died of apoplexy following hypertension. Her general health was excellent until the age of 23 when she began to complain of pain in her right flank and groin which at times became severe. Cystoscopic examination was made. Marked ptosis of the right kidney with slight hydronephrosis was found in Roentgen ray photographs. Following this procedure the attacks recurred, coming on as often as twice a month, relieved by cystoscopy with catheterization of the renal pelvis. The frequency of the attacks gradually became less over the next few years, but during the past 2 became greater.

Her blood pressure was first found elevated at the age of 24 and a few months later headaches appeared. At the age of 25 her systolic blood pressure was 180 mm. Hg.; at 27 it was 240, and at 28 her systolic was 198, her diastolic 136 mm. Hg.

In 1934, when she was admitted to this hospital, the physical examination was not remarkable. There was moderate obesity. The ocular fundi were normal. The heart was slightly enlarged in Roentgen ray photographs. The peripheral vessels were not thickened. The clearance of urea was 119% of normal and the maximal specific gravity of the urine was 1.036. There were no albuminuria or abnormal microscopic elements except for a few hyaline casts. Her basal metabolic rate was —25% of normal. After 2 weeks' rest in bed her blood pressure fell from a level of 200 mm. Hg. systolic, and 135 mm. Hg. diastolic, to 160 and 95, but rose again when she became active.

Four years later, when she was 32, her systolic blood pressure remained at a level of 190; her diastolic at 130 mm. Hg. The heart was slightly larger in Roentgen ray photographs. The ocular fundi were normal. The clearance of urea was 115%, and the maximal specific gravity of the urine was 1.031. There was a small amount of albuminuria and many white blood cells in the urine. The basal metabolic rate was —20%.

Pyelograms after intravenous injection revealed an apparently normal left renal pelvis and ureter. On the right, the kidney was markedly ptotic, the pelvis being small and contracted, and situated below the iliac crest.

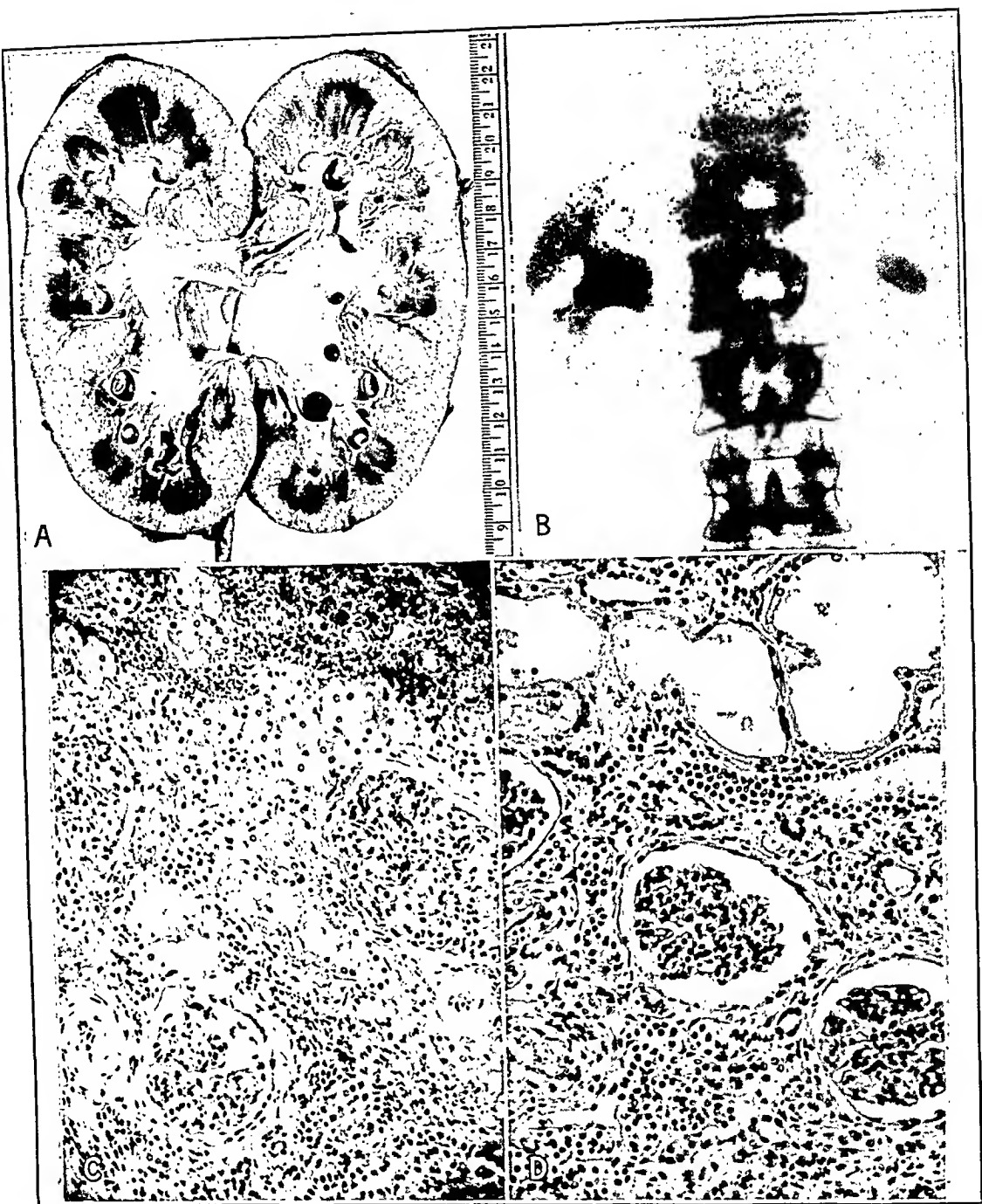


FIG. 1.—Case 1. *A*, Right kidney removed at autopsy, showing almost complete obliteration of cortex; *B*, pyelogram after intravenous injection, showing calculus in left renal pelvis, and slight degree of hydronephrosis on right; *C*, microphotograph of left kidney. Note advanced vascular disease, tubular atrophy, and infiltration of parenchyma with lymphocytes. *D*, Microphotograph of right kidney. Some of the tubules are dilated, the glomeruli are shrunken, and there is very little disease of arteries and arterioles.

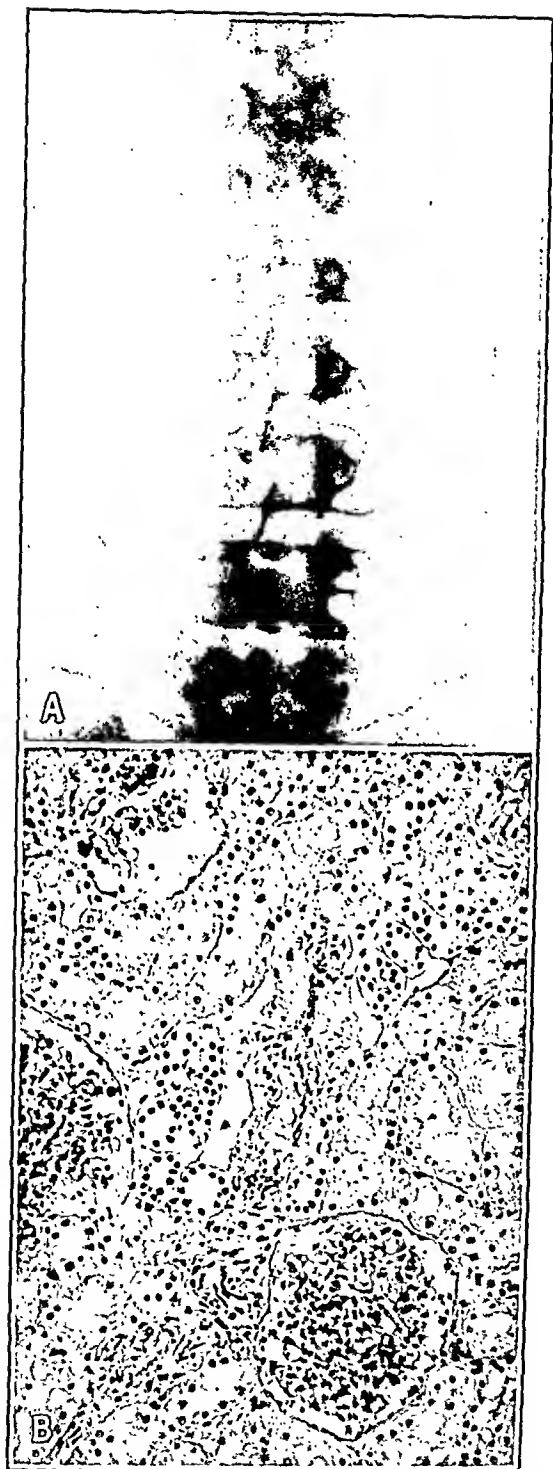


FIG. 2.—Case 4. A, Pyelogram after intravenous injection, showing ptosis and distortion of right renal pelvis; B, microphotograph of a section from the right kidney. Vascular disease is moderate and there is some fibrosis of the parenchyma.

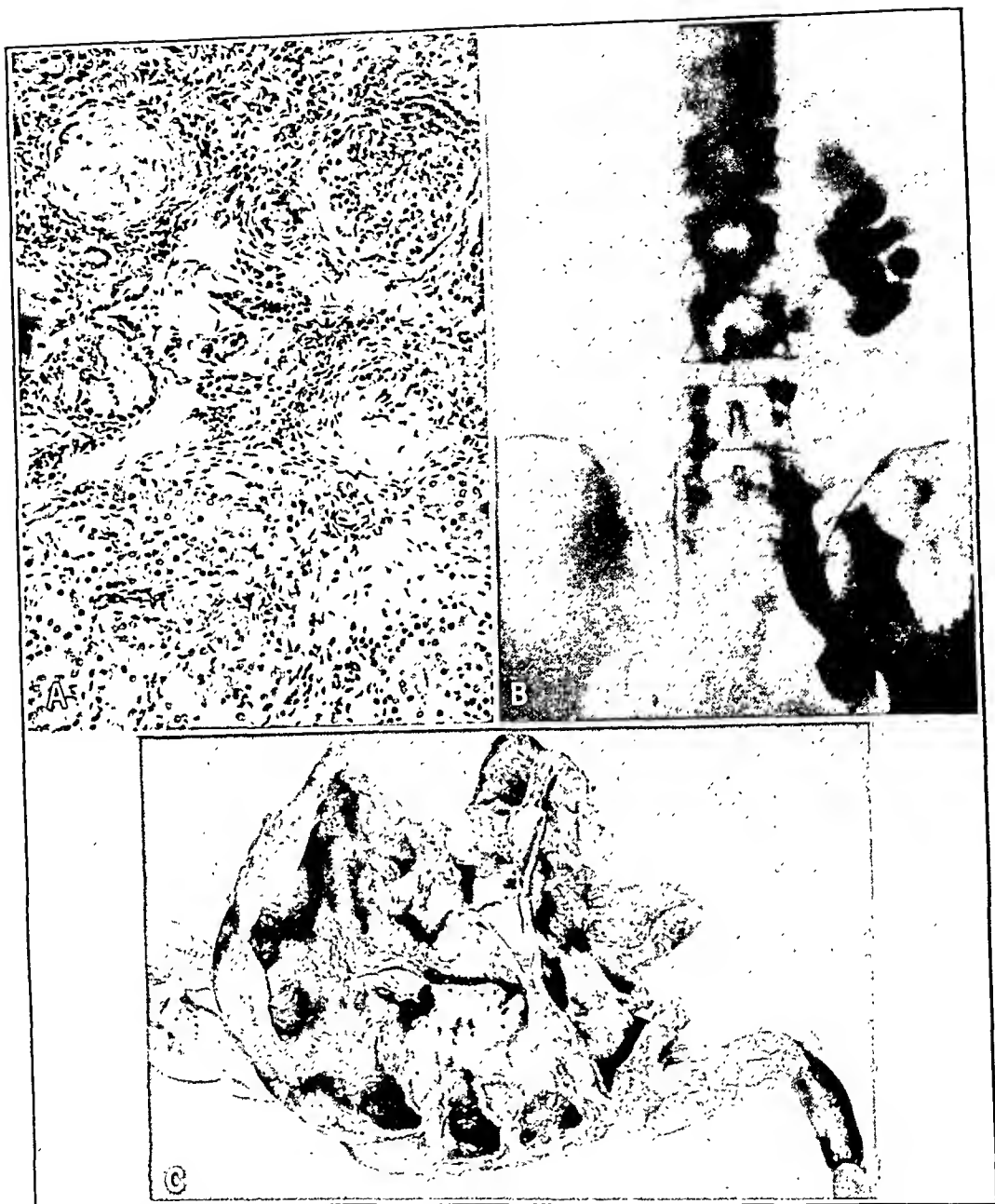


FIG. 3.—Case 6. *A*, Microphotograph of left kidney. There is fibrosis, atrophy of tubules and glomeruli, and lymphocytic infiltration, with minimal involvement of arterioles. *B*, Retrograde pyelogram of left kidney, showing hydronephrosis and hydro-ureter. *C*, Photograph of this kidney, showing almost total destruction of parenchyma. Section has been removed from the upper border.





Cystoscopic examination was therefore performed in October, 1938, and again in February, 1939, and the function of each kidney ascertained as follows:

	1938.		1939.	
	Right.	Left.	Right.	Left.
Phenol red excretion (10 min., 1938; 75 min., 1939) . . . . .	2.9%	12.1%	16.1%	34.8%
Clearance of urea . . . . .	21.0%	88.0%	28.0%	53.0%

Because of repeated attacks of pain in the right flank, nephrectomy on the right side was performed at the Squier Urological Clinic, June 10, 1939. The kidney was low in position, the ureter short, and the vessels entering the hilus elongated. The kidney itself was smaller than normal. Her blood pressure fell after operation to 138 systolic, 90 diastolic, but one month later it had risen to its preoperative level, where it has remained.

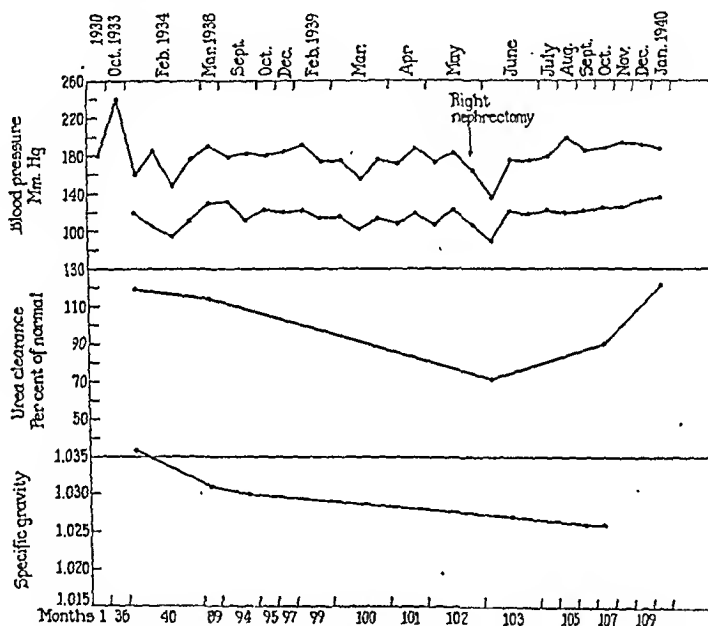


CHART 4.—Showing course of Case 4. Notations same as Chart 1.

*Description of Specimen.* The kidney was small and atrophic, and a large artery and vein ran in a tortuous oblique course across the upper anterior portion. There were also two aberrant renal arteries, one at the upper and one at the lower pole. The pelvis was distorted, but the cortex was of normal thickness, except where several fibrous bands extended to its surface. On microscopic section, Bowman's capsule was moderately thickened, and there was marked narrowing of the lumina of the smaller arteries and arterioles owing to sclerotic changes. Considerable fibrosis was evident.

*Comment on Case 4.* Arterial hypertension was associated with a unilateral renal affection which probably preceded the elevation of blood pressure. Although total renal function was normal, it was diminished in the affected kidney which was contracted and ptotic. Removal of this kidney 9 years after the onset of hypertension resulted in no change in blood pressure. Disease of the renal arteries was marked.

CASE 5.—(Hosp. No. 10,399). The case of F. C., a 26-year-old housewife, was similar. Her mother suffered from arterial hypertension. During childhood she developed chronic urinary infection said to have been pyelitis. At the age of 25 she experienced considerable emotional stress and began to notice marked nervousness. Her blood pressure was then found to be elevated, being 192 systolic and 130 mm. Hg. diastolic. Her heart was not enlarged. The ocular fundi were of normal appearance. Maximal specific gravity of the urine was 1.025, with slight albuminuria and cylindruria. Clearance of urea was 87% of normal. Retrograde pyelograms showed a small renal pelvis on the right, the calyces of which were club-shaped and distorted. Studies of the separate functions of the two kidneys were as follows:

	February, 1938.		September, 1938.	
	Right.	Left.	Right.	Left.
Phenol red excretion (10 min., Feb.; 30 min., Sept.) . . .	0.4%	3.8%	1.3%	14.3%
Clearance of urea . . . . .	17.0%	34.0%	3.0%	36.0%

Her systolic blood pressure then varied from 212 to 192, and her diastolic from 142 to 122 mm. Hg.

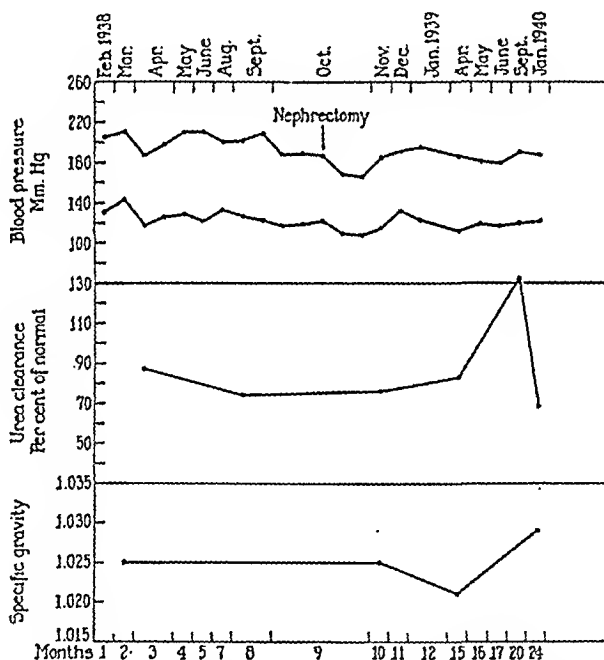


CHART 5.—Showing course of Case 5. Notations same as Chart 1.

The right kidney was removed on October 18. It was small (25 gm.), hypoplastic, scarred, and densely bound down by perirenal and peripelvic adhesions. There was a large aberrant artery entering the upper pole. Immediately following operation her blood pressure fell to almost normal levels, but one month later her systolic pressure, during rest in bed, varied from 200 to 170, her diastolic from 124 to 98 mm. Hg. There was no change in renal function. During the next 16 months her systolic pressure varied from 196 to 180, and her diastolic from 136 to 114 mm. Hg. She has complained of no symptoms.

*Anatomic Diagnosis of Kidney.* Arteriolar sclerosis, moderate to severe; fibrosis of kidney; (?) chronic pyelonephritis, healed.

*Comment on Case 5.* Arterial hypertension was associated with a unilateral contracted kidney, which may have been the seat of chronic pyelonephritis sustained in childhood. Removal of this kidney resulted in a temporary fall in blood pressure. There was moderately advanced vascular disease in the affected kidney. The course of the disease does not appear to have been influenced.

CASE 6.—(Hosp. No. 10,523). G. R., a 33-year-old electrician, was known to have suffered from arterial hypertension for 3 years. His past history was uneventful. At the age of 28 his systolic pressure was 134 mm. Hg. and his diastolic 84; at 29, 138 and 90; at 30, 145 and 112; at 31, 138 and 110. In April, 1938, at age 32, it varied from 170 to 182 systolic and 130 to 144 mm. Hg. diastolic, and he was therefore, referred to this hospital (R. I. H.) complaining of daily headaches and excessive fatigue.

On examination, there was little of importance to be made out. His ocular fundi were not remarkable. His systolic blood pressure was 192 mm. and his diastolic 138. He was admitted August 14, 1938. The vessels of the retina were then seen to be hazy and indistinct along their margins. Maximal specific gravity of the urine was 1.025, and there was moderate albuminuria and cylindruria. Pyelograms after intravenous injection demonstrated ptosis of the right kidney with slight hydronephrosis and angulation of the ureter; none of the radio-opaque medium was excreted by the left kidney. Cystoscopic examination was therefore performed on October 11, and retrograde pyelograms showed a huge hydro-ureter and hydronephrosis on the left, with constriction at the uretero-vesical junction. Studies of the functions of the two kidneys were as follows:

	Right.	Left.
Phenol red excretion (36 min.) . . . . .	9.3%	0
Clearance of urea . . . . .	50.0%	13%
Albumin . . . . .	0	++

In the ocular fundi at this time were slight papilledema and definite perivascularitis without exudate or hemorrhage. The clearance of urea was 82% of normal. A reaction to cystoscopy ensued, with fever, pain, and colic on the left side, which he stated was similar to an attack suffered at the age of 14. He was therefore transferred to the Squier Urological Clinic where left nephrectomy was performed on October 24, 1938. The kidney was densely adherent to the surrounding structures and the large and small intestines were bound down to the region of the renal pelvis. There was marked multiple angulation of the upper third of the ureter, which was dilated, thickened, and covered with fibrous bands. His blood pressure fell immediately to normal levels and his convalescence was uneventful. During the next 16 months his systolic pressure varied between 150 and 130, and his diastolic between 100 and 90 mm. Hg. He has noticed complete disappearance of headaches, has gained 9 kg. in weight, and no longer complains of fatigue.

*Description of Specimen.* The kidney weighed 60 gm. It was almost completely fibrotic. Very little renal tissue could be made out on gross inspection. The calyces were dilated and rounded, and the fibrous parenchyma was thickened. On microscopic section, marked fibrosis was seen, with perivascular lymphocytic infiltration. In certain areas glomeruli appeared normal, but many were congested and in the region of the scars none could be seen. There were purulent casts in the few tubules visible. The vessels were only slightly thickened as regards their intima and media.

*Anatomic Diagnosis.* Chronic pyelitis; hydronephrosis and hydro-ureter; fibrosis and atrophy; focal suppurative pyelonephritis; arteriolar sclerosis, minimal.

*Comment on Case 6.* Arterial hypertension was associated with advanced left hydronephrosis and hydro-ureter, with constriction at the uretero-vesical junction. There were also right nephroptosis, ureteral angulation, and slight hydronephrosis. Removal of the severely damaged kidney has resulted in a marked and sustained fall in blood pressure for a period of 16 months. The course of the disease has been unquestionably altered. Only minimal vascular disease was present in the kidney.

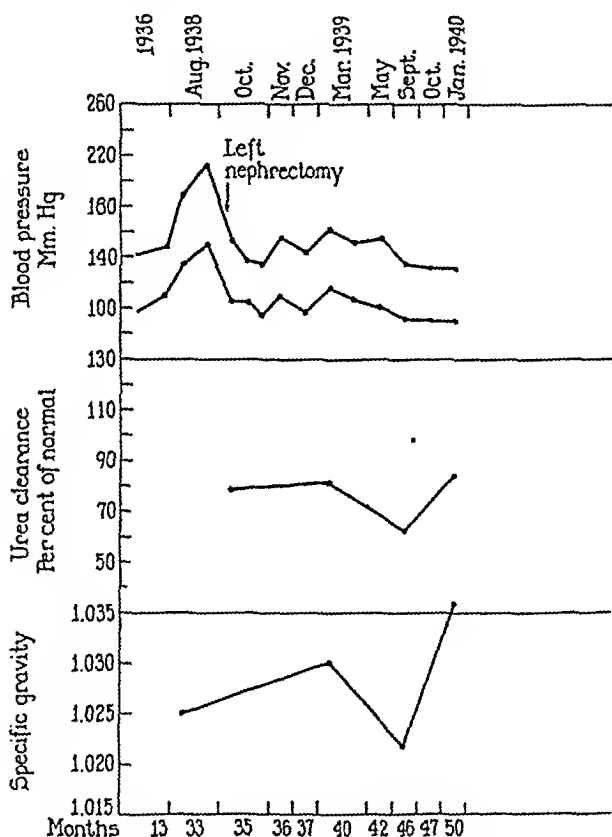


CHART 6.—Showing course of Case 6. Notations same as Chart 1.

CASE 7.—(Hosp. No. 10,475). A similar event was seen in M. A. a 20-year-old stenographer. At age 19, because of the complaint of increasing nervousness and palpitation following the death of her father, she was examined and her blood pressure was found elevated. She complained only of occasional headaches.

In May, 1938, the ocular fundi showed haziness of the nasal margins of both optic disks. The heart was slightly enlarged. Renal function was normal. Her systolic pressure varied from 220 to 194, her diastolic from 140 to 130 mm. Hg. Cystoscopic examination was performed; the left kidney was able to excrete 10.5% of the injected phenol red in 20 minutes, the right, only 0.8%. Retrograde pyelograms showed that the upper calyx of the right renal pelvis was blunted and club-shaped, and only two calyces were present.

Cystoscopic examination was repeated in February, 1939, and the functions of each kidney measured separately:

	Right.	Left.
Phenol red excretion (30 min.) . . . . .	0.5%	5.8%
Clearance of urea . . . . .	21.0%	54.0%

The total clearance of urea was 100% of normal, and maximal specific gravity of the urine was 1.032. Her blood pressure was at a slightly higher level.

The right kidney was removed on March 24, 1939. It was found to be adherent to the surrounding tissues about its upper pole, which was scarred. Three months after operation her systolic pressure varied from 172 to 142 and her diastolic from 96 to 80 mm. Hg, at which levels they have remained. Renal function has remained normal. The most marked change to be noticed was the diminution of emotional instability. Instead of being a tense, excited, hysterical, uncoöperative individual, she had become quiet, apparently well-balanced, and moderately relaxed. This change of personality was noted immediately after operation and has persisted.

*Description of Specimen.* The kidney weighed 70 gm. Its surface was smooth, but it was small and about the upper pole were two depressed scars. On microscopic section only a minimal amount of vascular disease was seen. There was some fibrosis of the parenchyma, but glomeruli and tubules were of a normal appearance.

*Anatomic Diagnosis.* Hypoplasia of kidney; scarring of upper pole; arteriolar sclerosis, early.

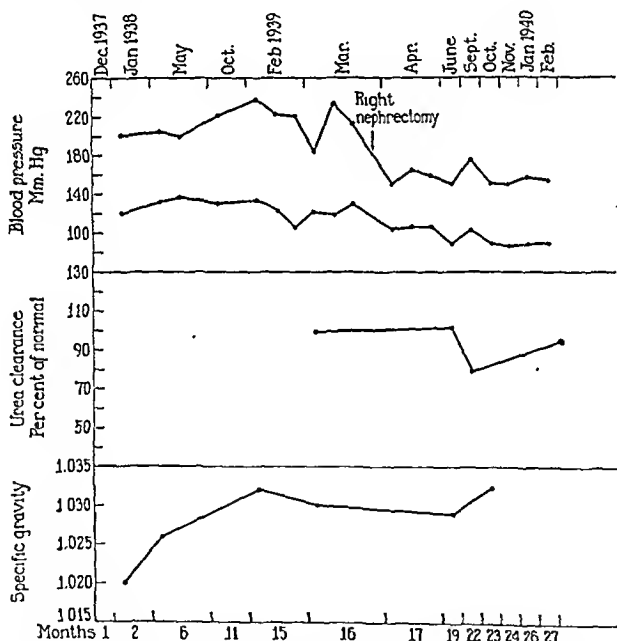


CHART 7.—Showing course of Case 7. Notations same as Chart 1.

*Comment on Case 7.* Arterial hypertension in a nervous young woman accompanied an undiagnosed condition of the right kidney. There was poor function of this kidney as compared with the left, and the renal pelvis was distorted. Removal of this kidney resulted in a lower level of blood pressure for 11 months.

*Discussion.* It is clear from these cases that removal of a diseased kidney does not consistently alter the course of arterial hyperten-

sion in a favorable direction. Only 2 cases were strikingly improved. These results indicate: 1, that the injured kidney was not the sole source of hypertension; and, 2, that other factors may occasionally be less important than the renal one. In every instance, however, removal of a kidney was followed by lowering of the level of the blood pressure for periods of weeks or months. It is difficult to believe that any major surgical procedure would have produced

TABLE 2.—SUMMARY OF CASES.

Case No.	Name.	Sex.	Age at onset and duration previous to operation* (yrs.).	Ocular fundi.†	Preoperative range of B. P.‡	Postoperative range of B. P.	Last recorded B. P.	No. of mos. follow'd.§	Renal lesions.	Degree of renal vascular disease.	Remarks.
1	H. S.	♂	33 1	Hem.++ Scar+ A-S+	210/130 180/120	244/140 200/130	138/80	8	Left hydronephrosis, pyelonephritis and calculus. Rt. hydronephrosis and infection	++++(L) +(R)	No improvement. Death from cardiac and renal failure
2	B. W.	♀	21 8	Scar+ A-S++++	260/150 210/120	240/140 170/120	240/140	5	Left pyelonephritis	++++(L) ++++(R)	No improvement. Death from renal failure
3	A. L.	♀	24 5	Scar+ A-S+ P-V+	230/150 196/126	200/120 120/80	182/110	23	Marked left hydronephrosis. Moderate right hydronephrosis, with ptosis	+++	Somewhat improved. B. P. considerably lower for 6 months
4	M. B.	♀	22 11	A-S++	190/135 170/100	190/125 180/120	192/124	8	Right ptosis and contracted kidney	+++	No improvement
5	F. C.	♀	<25> 1	Normal	212/142 192/122	200/124 140/90	182/122	16	? right pyelonephritis	+++	Sl. improvement in level of B. P.
6	G. R.	♂	30 2½	Pap.+ P-V+	212/150 190/138	150/100 120/80	132/90	16	Marked left hydronephrosis and hydro-ureter. Slight rt. hydronephrosis and ptosis	+	Considerable improvement
7	M. A.	♀	19 1½	Normal	240/150 194/120	150/100 120/90	150/100	11	? right pyelonephritis	+	Improvement to present time

\* i. e., of hypertension.

† Hem. = hemorrhage; Scar. = scarring; A-S = arteriosclerosis; P-V = perivasculitis; Pap. = papilledema.

‡ Figures indicate average levels of blood pressure during a period of several days; single high or low readings are not noted. Upper figure is highest level; lower figure, lowest level maintained under observation.

§ Since operation.

this result, since in some cases the improvement was prolonged, and in one instance (Case 3) operation of a much more extensive nature (partial gastrectomy) was followed by a rise in blood pressure. Some change in the pathologic physiology of the circulation occurs after nephrectomy, which we believe is due to removal of one factor at least causing hypertension.

All kidneys removed from these patients showed, in addition to a variety of lesions, inflammatory and non-inflammatory, varying degrees of arterial and arteriolar sclerosis. An attempt to grade the degree of vascular disease (Table 2) indicates that the least amount was found in those cases in which the best results were noted

(Cases 6 and 7). It is not certain, however, that the degree of vascular disease in one kidney is the same as that in the other, there being a marked difference in Case 1. With the exception of Case 3, in which there was prolonged but temporary improvement, favorable results appeared proportional to the amount of disease of the renal arteries.

Further evidence that renal lesions are not the sole cause of arterial hypertension is their presence when the arterial pressure is not elevated. Some other factor beside these lesions contributes to the genesis of hypertension. In addition, continuance of the elevated blood pressure after removal of the affected kidney may be explained by the part vascular or other disease in the remaining kidney plays. The 2 patients who have died exhibited pyelonephritis as well as vascular lesions. Recent investigation in rats has shown that vascular disease in the unaffected kidney follows partial constriction of one renal artery,<sup>13</sup> and Goldblatt<sup>7</sup> has demonstrated its presence in other organs after bilateral arterial constriction. The pathogenesis of arteriolar sclerosis in the kidneys of human beings remains, however, unsettled. The occurrence of this lesion in almost all cases of "essential" hypertension<sup>10</sup> is nevertheless well recognized. It is still uncertain whether arteriolar disease is secondary to the renal lesion in cases similar to these, although animal experiments suggest such a relation.

From this study it is obvious that removal of a diseased kidney is not to be regarded as a procedure from which relief of hypertension can be expected to occur in all or in many cases. If arteriolar disease is secondary to the renal lesion or to hypertension and serves to maintain an elevated blood pressure which was initiated in the first place by a renal lesion, it would appear possible sometimes to obtain improvement by nephrectomy. A successful result might be expected if the lesion were confined to one kidney, and if arteriolar sclerosis of the other kidney had not progressed to an irreversible degree.

We suggest therefore the following criteria for selection of cases suitable for this form of therapy:

1. The onset of arterial hypertension should be known to have occurred recently. We place the time arbitrarily at 2 years.

2. The renal lesion should be confined to one kidney and should be of such a nature that diminution of function has occurred in that kidney.

3. Renal functions, as measured by the ability of both kidneys to concentrate urine and by the test of the clearance of urea, should be within normal limits.

4. Retinitis should be absent, and changes in the caliber of the vessels of the retina minimal.

5. Arterial pressure should be persistently elevated.

These criteria were followed only in Case 7, the others having



exhibited either bilateral disease, hypertension of long duration, or some diminution of renal function. Unless suitable cases are selected, many kidneys may needlessly be removed (as in Cases 1, 2, and 4) without benefit. This experience has served to suggest that patients in whom long standing hypertension is present, or in whom a so-called "malignant" course has commenced are not good subjects for this form of therapy.

**Summary and Conclusions.** Seven patients exhibiting arterial hypertension associated with organic renal disease have been subjected to nephrectomy. Two were markedly improved, and 2 slightly improved, but all remain actually or potentially hypertensive.

This form of therapy may prove of benefit, but, it seems, only in patients in whom the existence of hypertension is of short duration and in whom arteriolar sclerosis of the other kidney is not advanced. Its use is limited, therefore, to a small number of individuals.

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## THE RÔLE OF THE KIDNEY IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION.

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IN the light of the experimental results obtained by Goldblatt and collaborators,<sup>7a-c,8-11</sup> and other investigators<sup>3,5,14,15a,b,16,19,21</sup> who have succeeded in demonstrating the probable part played by renal ischemia in hypertension, I wish to report in some detail the history of 2 patients recently observed.

**CASE 1.**—Gil. M., female, aged 30, was admitted to the hospital on Jan. 13, 1938, with almost total anuria, lumbar and polyarticular pains, severe headache and poor general condition. A week before, following an abortionist's manipulation, she had a temperature of 102° F. and generalized jaundice. Since then, had violent pains in the region of the kidneys and scarcely urinated any more. In the clinical examination, the pertinent findings were: a pale face and very dry lips; normal heart action; blood

pressure was 112/55; pulse 80 and regular; the breathing was irregular, reminiscent of the Cheyne-Stokes type, but the lungs were normal; ocular fundi were normal. The clinical examination revealed nothing significant, but the analysis of blood and urine was diagnostic.

Analysis of blood showed: urea, 456 mg.; chlorine, 255 mg.; calcium, 7.96 mg.; uric acid, 23.9 mg.; and  $\text{CO}_2$  combining power, 25.1 vols. per 100 cc. of plasma; red corpuscles, 1,460,000; white corpuscles, 6400; hemoglobin, 25%. Urine analysis: dilute and contained only 1090 mg. urea, and 40 mg. chlorides per 100 cc.

The tests for renal function showed significant impairment; Ambard,  $K = 1.630$  (4.3% of normal); Van Slyke,  $C = 1.900$  (3.6% of normal); Rehberg,  $F = 9.760$  cc. per minute.

The intradermal injection of a drop of histamine and of acetyl-choline gave rise to normal zones of erythema (35 cm.<sup>2</sup> and 21 cm.<sup>2</sup>), and the dermographic latency period was normal (5 seconds).

To sum up, the patient, from an undetermined toxic cause, showed an almost complete abolition of renal secretion with enormous nitrogen retention, marked anemia, but no hypertension.

Ten days after admission, the azotemia was still very high; the highest level of urea reached during this period was 527 mg. The output of urine gradually increased to well above 1000 cc. in 24 hours, but without any improvement in the concentration, which remained, on the whole, comparable to what it was at the beginning. Four days later, tests for renal function showed very slight improvement.

The striking thing is that, in spite of the intense and prolonged nitrogen retention, the arterial pressure showed no tendency to rise; it remained at 115/55. Correspondingly, the zones of erythema following the intradermal injection of a drop of histamine or of acetyl-choline remained normal, and the period of dermographic latency remained at 5 seconds.

Slowly the patient's condition improved. About a month after her admission, N.P.N. was 30 mg., and Ca was 10.2 mg. per 100 cc. of plasma, but uric acid remained high, 11 mg. per 100 cc. The anemia slowly improved; red corpuscles, 2,880,000 per cm. Eventually, the urinary secretion also improved; about 2000 cc. in 24 hours, and the concentration was better. At this time renal function tests showed: Ambard,  $K = 0.140$  (50% of normal); Van Slyke,  $C = 27.07$  (37% of normal); Rehberg,  $F = 74$  cc.

In this condition the patient left the hospital at the end of 7 weeks. She has been seen periodically, and the improvement has continued, but extremely slowly. Altogether, 6 months were necessary to restore her health. At the present time, *i. e.*, after 12 months, the function of the kidneys has become completely normal. The arterial pressure, which did not vary during the whole course of the nephropathy, remains low, at about 120/55. The anemia has entirely disappeared.

CASE 2.—Pi. A., female, aged 28, was admitted to the hospital on Dec. 21, 1937, for palpitation of the heart that occurred after the least effort. This condition, which dated back 2 years and began after an attack of scarlet fever, prevented the patient from doing work. A physician, consulted a year ago, is said to have found albuminuria in very slight quantities and prescribed an appropriate regimen with rest. Suddenly, 2 months before admission, during the night, there occurred an attack of suffocation and anxiety which lasted, according to the patient's statement, several hours. This recurred, always in the night. For 2 months there was also frequent migraine, accompanied by black scotomata and noises in the ears.

The patient lay calmly in bed, showing neither cyanosis nor any trace of edema. The heart, on percussion, was slightly enlarged. On auscultation, a gallop rhythm and metallic second sound were heard. The pulse was tense, arterial pressure high, 220/142. The examination of the abdomen

and of the nervous system revealed no abnormality. The ophthalmoscopic examination showed old scars of exudative retinitis and abnormally contracted arteries.

Analysis of the blood showed: urea, 25 mg.; calcium, 10 mg.; glucose 98 mg.; uric acid, 3.8 mg.; cholesterol, 142 mg.; and  $\text{CO}_2$  combining power, 52 vol. per 100 cc. of plasma. Urine: no albumin, no sugar and microscopic examination negative. Renal function tests: Ambard,  $K = 0.0520$  (134% of normal); Van Slyke,  $C = 123\%$  of normal; Rehberg,  $F = 165$  cc. per minute. Reactions of the peripheral vessels: dermatographic latency period, 2 to 3 seconds; areas of erythema, to histamine, 21 cm.<sup>2</sup>, and to acetylcholine, 13 cm.<sup>2</sup>

This condition remained without appreciable change during the whole period of her 6 weeks' stay in the hospital. Arterial pressure remained unchanged at a high level; signs of vascular spasm were always present, and renal function remained excellent. The patient was seen again 10 months later in a state of obvious physical distress. There was marked emaciation. On the body were seen purpuric spots and numerous ecchymoses. The heart beat was forcible and irregular. Arterial pressure was 235/162. There was no visible edema. The lungs were full of râles, due to stasis, and there were numerous transient crises of acute edema of the lungs. The urine contained minute traces of albumin; the microscopic examination showed numerous white corpuscles, some red corpuscles, and rarely, some casts.

The renal function tests were still within the limits of normal. The blood analysis, however, showed a slight increase of uric acid, 5.9 mg. per 100 cc.; whereas the N.P.N. remained about normal, 34 mg. per 100 cc. The blood count revealed a marked anemia, 2,100,000 red corpuscles. The alkali reserve was low, 38 vol.  $\text{CO}_2$  per 100 cc.

Investigations of the state of vasoconstriction of the peripheral vessels showed: dermatographic latency period, 2 to 3 seconds; areas of erythema, to histamine, 16 cm.<sup>2</sup>, and to acetylcholine, 10 cm.<sup>2</sup>

We then lost sight of this patient.

To sum up, then, we observed on the one hand a patient, who, after an intoxication of undetermined origin, had cessation of renal excretory function, without hypertension, and, on the other hand, a patient who, secondarily to scarlet fever, showed marked hypertension without, for a long time, any accompanying signs of renal excretory insufficiency.

**Discussion.** These 2 cases raise a number of problems that cannot be discussed within the limits of this paper. Only the blood pressure will be discussed. The problem is why the first of these patients, with marked renal excretory insufficiency, did not have hypertension, whereas the other, despite normal renal excretory function, did show a rise of blood pressure.

According to old ideas, the first patient, who showed an enormous nitrogen retention, should have had hypertension. In fact, a glance at the principal classifications of nephropathies reveals that diminution of urinary secretion and nitrogen retention develop, as a general rule, hand in hand with hypertension. This idea, however, is in contradiction with a series of experimental results. Neither the removal of both kidneys, nor the total ligation of both renal pedicles, nor the anastomosis end to end of a ureter and an iliac vein,

all of which produce marked nitrogen retention, causes any appreciable rise of arterial pressure.<sup>7b,c,1,2,4c,18</sup> As for the hypertension observed after occlusion of both ureters,<sup>4e,f,j,12,13</sup> it seems that it is in no way due to the retention of products of metabolism. Therefore, one may conclude that whatever the cause of nitrogen retention may be, the latter is not able to raise the arterial pressure.

What then are the necessary and sufficient conditions for the development of persistent hypertension? We know that in the course of hypertensive nephritis, malignant hypertension and angioneurosis, the power of the peripheral vessels to dilate in response to histamine<sup>6</sup> and acetyl-choline is diminished,<sup>4a,d-f,20</sup> and that this peripheral vasoconstriction is not pathognomonic only of rises of arterial pressure accompanying kidney disease, but that it exists also in the course of transient diseases (scarlet fever, streptococcal tonsillitis) in the absence of any impairment of renal excretory function.<sup>4a,b,d</sup> Simultaneously with a diminution in the power of dilatation, it can be shown, in these circumstances, that there is an increase of vascular tonus,<sup>4o,h</sup> and, as Kylin<sup>17</sup> demonstrated long ago, an increase of pressure in the capillaries. This triad of vasoconstrictional symptoms is the expression of a spastic state of the peripheral vessels.

But what is the determining factor in this spasm? Goldblatt and his collaborators<sup>7a-e,8-11</sup> produced chronic renal ischemia by constricting the main renal arteries with silver clamps, and found that the hypertension that followed could be independent of any significant impairment of renal excretory function and varied in proportion to the degree of the constriction. Only when the constriction of the renal arteries was very great did uremia develop. These excellent experiments of the American investigators, which have been repeated and verified many times by numerous authors, have cast a fresh light upon the pathogenesis of the hypertension accompanying diseases of the kidneys. These experiments have shown that for the kidney to be able to produce and maintain hypertension it is necessary and sufficient that its circulation be reduced. It has been shown in various ways<sup>4i,j,d,7b,14,15a,b,16</sup> that this type of hypertension is not of nervous origin, but rather the result of a humoral mechanism. It is very likely that as a consequence of the slowing up of the irrigation of the kidney with blood, certain chemical processes of disintegration or of synthesis are no longer carried to their normally harmless conclusion, and that the decrease of combustion gives rise to products which, reabsorbed by the circulation, act directly or indirectly upon the peripheral vessels. For example, the ischemic kidney does not possess the same power of hydrolyzing saccharose or of reducing methylene blue or other dyestuffs at a corresponding pH (Dicker<sup>4j</sup>, and it is at least possible that this diminution in the power of hydrolysis and reduction may be the source of production of substances which, when absorbed

by the blood stream, may, directly or indirectly, cause a generalized vasoconstriction.

If this view be correct, that the kidney is an organ capable of producing hypertension without any accompanying significant alteration of its excretory functions, we must henceforth separate the hypertension observed in the course of certain nephropathies from other functional renal lesions, and regard the problem of the hypertension accompanying nephritis as being the result of alteration of functions that are independent of those involved in the elaboration of urine. At the same time, we should be able to understand why hydronephrosis or pyonephrosis, with or without increased azotemia, may develop without an accompanying rise of arterial pressure, unless, as is frequently the case, the kidney is also the seat of vascular disease.

By applying these ideas to the histories of our 2 patients, we can understand at once why the first patient, who had virtual cessation of renal excretory function, with enormous concomitant azotemia, did not suffer from hypertension, whereas the other, in whom all the renal excretory functional tests were normal, showed an appreciable rise of arterial pressure.

The first, indeed, showed no signs of peripheral vasoconstriction. One can, without much risk of being mistaken, assert that whatever the toxic agent was that had caused the abolition of urinary secretion, it did not at any time reduce the normal irrigation of the kidneys with blood.

In the other patient, on the contrary, it is the peripheral vascular spasm which dominated the picture. The probability is great, although not actually proved in this case, that the kidneys were the seat of arteriolar disease.

These 2 cases demonstrate that the hypothesis that nitrogen retention is a cause of hypertension is untenable and indicate that the diminution of renal irrigation with blood is a sufficient condition to cause and maintain hypertension.

**Conclusion.** For the kidneys to be able to cause hypertension their circulation must be restricted; all the other renal and urinary manifestations are secondary, independent and incapable of playing a part in the production and maintenance of the hypertension.

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## ESSENTIAL HYPERTENSION.

### A COMPARISON OF THE HYPERTENSIVE AND NON-HYPERTENSIVE PHASES FOLLOWING CORONARY THROMBOSIS.

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It has been generally accepted that in the hypertrophied heart not resulting from primary valvular, deficiency or kidney disease, hypertension is the major, if not the sole cause of cardiac enlargement.<sup>2</sup> The association of hypertension with coronary disease is well known.<sup>1,9</sup> Furthermore, the chronic phase of congestive heart failure of all types usually occurs in the end-stage of cardiac hypertrophy.<sup>12</sup> If hypertension is so frequently associated with coronary disease and is the cause of cardiac hypertrophy, the question arises whether a fall in blood pressure following coronary thrombosis might not exert a beneficial effect on the subsequent course of the disease, especially if it could be established that the blood pressure remained low for years following such a vascular accident.

**Method.** In order to establish the effect of either a restoration or a permanent drop in blood pressure following coronary occlusion, 100 hypertensive cases were reviewed at postmortem. Only known hypertensive cases were chosen in which the existence of previous coronary thrombosis and myocardial infarction were confirmed by necropsy. The rôle of the blood pressure on the subsequent course of coronary disease, heart weight and heart failure was studied. Only those in which the blood pressure was frequently observed for at least 1 year prior to death were included since isolated blood pressure readings have little significance. Those associated with chronic disease like tuberculosis or malignancy were eliminated so as to obtain as clear a picture as possible of the effect of a fall or persistence of hypertension following coronary occlusion. The use of stringent criteria unfortunately narrowed down the material to a relatively small number of

cases. It is to be emphasized that due to the type of patient admitted to the hospital, the material does not represent a survey of hypertension but of advanced heart disease associated in the majority of instances with chronic congestive heart failure.

**Findings.** There were 31 females and 69 males. The average age at death of the males was 59.6 years; of the females, 62.3 years.

In 44 cases it was possible to determine the exact date of the acute coronary thrombosis either from a definite clinical course indicative of such an episode or from permanent electrocardiographic changes. In 19 of these persistent hypertension recurred within several months. In 15, the blood pressure remained permanently low subsequently, and in 10 the blood pressure varied. Listed chronologically as to duration of life following acute coronary thrombosis there were:

Up to 6 months . . . . .	6	2 to 3 years . . . . .	5
6 to 12 months . . . . .	4	3 to 5 years . . . . .	8
12 to 24 months . . . . .	15	More than 5 years . . . . .	6

The longest duration of life was 9 years.

In 56, no exact date of a coronary occlusion could be determined. In many of these, anginal pain was present anywhere from several months to 20 years. Though the diagnosis was often suspected, unless the clinical or cardiographic picture was clear the case was not put in the group of clinically diagnosed acute coronary occlusions.

It is interesting to note that in 25 cases there was no history of any cardiac pain, similar to the cases of silent coronary thrombosis reported in the literature.<sup>14</sup>

In 24, a terminal acute coronary thrombosis was found frequently as the cause of death or responsible for rapidly progressing terminal failure. All had previous old occlusions. In addition, 21 patients died very quickly. Many of these had the picture of an acute coronary occlusion which was, however, only found at necropsy in 4 cases. The others were instances of what Levy and Bruenn<sup>10</sup> called acute coronary insufficiency. Since some patients with the picture of an acute coronary closure at necropsy had no recent coronary occlusion, and others with no symptoms had coronary disease, the necessity of studying postmortem material is apparent.

Chronic congestive heart failure was present in 90 cases. In 24, failure occurred directly following an acute coronary thrombosis that was diagnosed.

Duration of failure in chronic obstructive coronary disease:

Up to 6 months . . . . .	7
6 to 12 months . . . . .	7
1 to 2 years . . . . .	30
2 to 3 years . . . . .	18
3 to 5 years . . . . .	21
Over 5 years . . . . .	7
Total . . . . .	90

Failure lasted approximately as long in the group in which an exact date of an acute occlusion was available as in that which the time of the vascular lesion could not be fixed.

TABLE 1.—RELATION OF BLOOD PRESSURE TO HEART FAILURE AND WEIGHT OF HEART.

Duration of failure.	Date of acute coronary occlusion known.			Date of acute coronary occlusion unknown.			
	Weight of heart in grams.						
	Persistent hypertension.	Persistent low blood pressure.	Varied.	Persistent hypertension.	Persistent low blood pressure.	Varied.	Average.
Under 1 year	475 700 650	400 480 ..	400 580 ..	640 630 430	600	280	522
1 to 2 years	500 490 480 500 630 430	760 510 650 690 .. ..	500 450 500 600 .. ..	570 600 500 400 680 ..	450 600 500 670 550 470	620 850 600 500	560
2 to 3 years	500 610 850 500 410 460	630 500 .. .. .. ..	400 380 620 .. .. ..	430 640 570 700 650 530 420	320 .. .. .. .. .. ..	600 300 .. .. .. .. ..	525
Over 3 years	900 470 500 550 .. .. .. ..	550 740 590 680 .. .. .. ..	840 .. .. .. .. .. .. ..	530 620 700 750 540 500 400 400	420 600 530 470 580	450 580 550 800 550	583
Average weight	558	599	527	558	521	557	

In Table 1 an attempt has been made to study the effect of the factor of blood pressure on the course of congestive heart failure, and of both these factors on the heart weight at postmortem. The cases in which a date of an acute coronary occlusion was known, as well as those in which it was not known, were divided according to whether hypertension persisted, remained low or varied. It mattered little whether the blood pressure was high, low, or varied. No essential difference was noted in the subsequent course of the patients.

The duration of life similarly did not seem to be dependent upon the course of blood pressure following the acute occlusion as will be observed from the following table:

TABLE 2.—DURATION OF LONGEVITY TO LEVEL OF BLOOD PRESSURE FOLLOWING CORONARY CLOSURE.

	High.	Low.	Varied.
Up to 1 year	3	4	3
1 to 2 years	6	2	4
2 to 3 years	5	3	1
Over 3 years	5	4	2
	19	13	10



In 2, the dates of the acute closure could not definitely be determined. These are left out of the above tabulation. The longest duration of life was 9 years. In this case the blood pressure was persistently elevated.

As may be observed from Table 1 neither the level of blood pressure following coronary occlusion nor the duration of congestive heart failure materially affected the heart weight at necropsy. It is evident, then, that no exact correlation is possible between the duration of failure and heart weight except that failure occurred in the enlarged heart.

TABLE 3.—CAUSES OF DEATH.

	Cases.		Cases.
Progressive heart failure . . .	41	Uremia . . . . .	6
Terminal acute coronary closure	24	Mesenteric thrombosis . . .	2
Cerebral thrombosis . . . .	7	Pulmonary infarct . . . .	2
Cerebral hemorrhage . . . .	1	Acute coronary insufficiency .	17

In the 24 cases of terminal acute coronary occlusion the course of blood pressure was known for at least 1 year prior to death. Fifteen had hypertension which persisted until the final closure, 7 had low blood pressure for months prior to closure, and in 2 the blood pressure had varied in the preceding year. Apparently, the blood pressure was not causally related to the terminal acute thrombosis. We cannot say, however, what the blood pressure was in the few days or hours preceding occlusion.

**Discussion.** We felt it necessary to study only the material in which coronary closure could be confirmed by necropsy. It is impossible to differentiate clinically many cases of acute coronary insufficiency from anatomical coronary occlusion, since electrocardiographic changes typical of coronary thrombosis may occur with short anginal seizures. On the other hand, instances of silent coronary occlusion are not infrequent. All the cases had advanced coronary arteriosclerosis and thrombosis, myocardial infarction and cardiac hypertrophy secondary to hypertension of varying duration. The use of postmortem material also afforded us the opportunity of studying the exact heart weight.

It has been shown<sup>3</sup> that in coronary thrombosis the incidence of antecedent hypertension may be as high as 90%. The associated cardiac hypertrophy is evidently due to hypertension. Advanced coronary disease and myocardial infarction may, however, occur in normal-sized hearts.<sup>11</sup> The distinguishing feature between cases with and without hypertension is that in those without hypertension the hearts are small. Local impairment of nutrition of the heart sufficient to cause infarction could on physiological grounds be looked upon as adequate cause of cardiac hypertrophy, but clinically does not occur in our experience. Since hypertension may permanently fall following coronary occlusion, or disappear for many years, or only be suspected from the associated renal or

fundus changes, it may be said that the hypertrophied hearts so commonly observed to be associated with chronic coronary artery disease is with few exceptions due to antecedent hypertension.

In the material studied, hypertension was established in every instance. The degree of cardiac hypertrophy did not parallel the duration or severity of high blood pressure. In some instances, despite severe hypertension of long duration, cardiac hypertrophy was not great. In a number, heart weight was at or below 400 gm. Since additional factors besides increased diastolic tension and augmented peripheral resistance play a rôle in the genesis of cardiac hypertrophy, the occurrence of hypertension of long duration with hearts of normal size is not surprising.

Ninety per cent of our cases had congestive failure. Such a marked proportion of failure is due to the fact that this hospital has an unusually large number of chronically ill cardiac patients in its wards. Failure was as severe in the group in which an exact date of coronary occlusion was known as in that in which it could not be determined. The course of chronic artery disease is naturally the same whether the date of occlusion is known or not. Furthermore, failure was as severe and as long in duration in the patients in whom the blood pressure fell to normal as in those in whom high blood pressure persisted. The heart weights were roughly the same in both groups regardless of the duration of failure. Evidently it was not the persistence of hypertension that caused the heart to go into failure in one group and not in another, but the big heart which failed in both. Irrespective of the severity of the vessel and muscle damage the common background of congestive heart failure in this material as in failure of all types is cardiac enlargement.

Palmer<sup>13</sup> was of the opinion that the prognosis was better in hypertensive cases in whom, following coronary occlusion, blood pressure returned to a high level. This view is not supported by our observations since we found that a restoration of hypertension did not adversely or beneficially affect the life span of the patients. Similarly, a persistently low blood pressure following coronary occlusion also neither adversely nor beneficially affected the clinical course of the patients.

The discrepancy between the cases in which hypertension recurred and those in which it did not is more apparent than real. Hypertension of long duration was present in both groups prior to the acute occlusion and caused the hearts to undergo varying but fairly marked degrees of cardiac enlargement. Vascular and myocardial damage were as severe in the one as in the other group. Both suffered from a primary impairment of nutrition due to coronary disease, and both suffered from a secondary impairment of nutrition due to cardiac hypertrophy. It has been shown<sup>5</sup> that in the thickened fiber the capillary bed is diffused over a greater area than in the normal, that the blood supply varies inversely as the square

of the distance from the capillary,<sup>7</sup> and that the pulse rate is not slowed in proportion to the degree of increased fiber size.<sup>6</sup>

The blood pressure shows marked variations with many factors and for long periods of time. It is also accepted that the blood pressure is not directly related to the functional capacity of the heart but is due solely to the peripheral resistance. Low blood pressure may be found with good cardiac function; high blood pressure may be found with marked failure as the heart for a long time overcomes the increased load.

To maintain the circulation, the heart must itself obtain ample blood. The blood supply to the heart depends upon many mechanical, humoral, and reflex factors. Normally, the heart is supplied chiefly during diastole, systole being of lesser importance. Increased systolic and diastolic blood pressure according to Gregg<sup>4</sup> augment coronary flow during acute hypertension; Kountz,<sup>8</sup> however, has recently shown that in the hypertrophied or dilated heart the major portion of coronary flow occurs during systole when the heart approximates its normal diastolic volume. In hypertrophied hearts, increase in systolic perfusion pressure corresponding to hypertension, did not augment coronary flow. Increasing dilatation progressively reduced coronary inflow.

In the patients in whom there was a restoration of hypertension the heart had to work against increased peripheral resistance, whereas when there was no such restoration, the cardiac load was less. If hypertension increases coronary flow one would expect a beneficial effect in such cases. Such benefit might be lost in the patients in a permanent drop of blood pressure but there is less work for the heart. The enlarged heart, however, requires the increased coronary flow associated with hypertension. On the other hand, the observations of Kountz would negate the views that the restoration of hypertension is beneficial by causing an increase in coronary flow.

In our patients, whether the high blood pressure recurred or not following coronary occlusion, the terminal heart weight, duration of heart failure, and the duration of life were the same. It appears to us that in the enlarged heart with preëxisting extensive vascular and myocardial damage, the nutrition to the heart itself is of greater importance in maintaining cardiac efficiency than the load the heart has to bear. The frequency with which a small vessel closure produces permanent congestive failure in a large but not in a small heart, and the number of cases of congestive failure associated at necropsy with a terminal small coronary occlusion attest to this fact. The occurrence of acute failure following a slight increase of the pulse rate in a hypertrophied heart is additional proof.

It is not possible to state why persistent hypertension which is so great a burden to the heart should, when it recurs following coronary occlusion in the enlarged heart, neither hasten further

myocardial damage nor failure. It is felt that in the presence of marked coronary disease, cardiac hypertrophy, and infarction the damage has been done and is the same whether high blood pressure recurs or not. Evidently physiological adjustments in coronary flow in both groups lead to the same natural course.

**Summary and Conclusions.** 1. An analysis is presented of 100 autopsied cases of hypertension and severe coronary artery disease studied for the effect of the blood pressure on the subsequent course. All the cases had cardiac hypertrophy and marked myocardial damage.

2. Ninety cases had chronic congestive heart failure. The high incidence of heart failure is partly due to the type of patient admitted to Montefiore Hospital. The onset of heart failure frequently followed an acute coronary occlusion. This occurrence was so striking that in cases of chronic coronary sclerosis when heart failure begins rather abruptly a silent coronary occlusion should be suspected.

3. There were 24 cases with terminal acute coronary closure and in these the course of blood pressure was known for at least 1 year prior to death. Fifteen had hypertension persisting up to the final closure, 7 had low blood pressure for several months prior to the closure and in 2 the blood pressure varied in the preceding year.

4. Analysis of the course of blood pressure subsequent to acute coronary occlusion was made. Eighteen cases had persistent hypertension (after recovery from the initial drop), 12 had permanently low blood pressure, and in 10 the pressure varied. The same variations in the course of hypertension occurred when no acute occlusion could be diagnosed clinically with certainty.

5. Twenty-one of the 100 cases died suddenly. Many of these had the clinical picture of acute coronary thrombosis but in only four of this group was a terminal closure found following coronary thrombosis.

6. The subsequent blood pressure in hypertensive cases following coronary thrombosis had no effect on longevity, or on the occurrence, severity and duration of heart failure. Neither was there a definite relation between the course of blood pressure and the heart weight and the duration of failure. Physiological factors undoubtedly play a rôle in adjusting the work of the heart to a restoration or a permanent fall in the blood pressure. These factors have been discussed.

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## PAINLESS MYOCARDIAL INFARCTION.

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DURING the past few years it has become apparent that the sudden occlusion of a large coronary artery is not always associated with the pain which commonly characterizes this accident. Obrastzow and Straschesko,<sup>10</sup> who first recognized coronary occlusion as a clinical and pathologic entity, emphasized the occurrence of three groups of symptoms: "status anginosus," or retrosternal pain often radiating to the left arm; "status gastralgicus," or pressure in the epigastrium; and "status dysnepticus," or dyspnea and respiratory irregularities. The work of Herrick<sup>6</sup> is mainly responsible for the great advances in the recognition and treatment of this disorder which have taken place in America during the last quarter of a century. In his original communication he made the interesting suggestion that sudden coronary occlusion due to thrombosis may result in more profound symptoms than gradual arteriosclerotic occlusion. He mentioned no cases of his own in which pain had been absent, but noted that other authors had reported cases of this kind.

In the numerous reports of small and large series of cases of coronary occlusion that have been published, the incidence of painless occlusion has varied greatly (Table 1). Some authors have included in the painless group all cases in which the patient did not use the term pain in describing his symptoms, even though "precordial discomfort," "precordial distress," or "a sense of constriction in the chest" did occur. Other authors have considered sensations of this kind as equivalent to pain and have defined painless coronary occlusion in such a way as to exclude all cases in which they occurred. Some authors have included in the painless group cases in which the patient had experienced transient anginal pain of the type which occurs in angina of effort, but no prolonged

pain of the sort usually considered characteristic of coronary occlusion and in which there were no dramatic symptoms at the time when, judging from the postmortem findings, the coronary occlusion was thought to have occurred. The number of cases of painless coronary occlusion encountered obviously depends upon how the term painless is defined and upon the care with which the history is taken. Furthermore, there is often great difficulty in differentiating the pain of angina pectoris and that of coronary occlusion.

TABLE 1.—INCIDENCE OF PAINLESS MYOCARDIAL INFARCTION AS PREVIOUSLY REPORTED.

Authors.	Cases studied.	Incidence of painless cases, %.	Remarks.
Boyd <sup>1</sup>	127	33	
Bruenn <sup>2</sup>	31	61	
Davis <sup>3</sup>	42	50	53 cases reported; 11 died suddenly (not included here).
Gorham and Martin <sup>4</sup>	100	42	"Vague discomfort or a sense of pressure or constriction in the chest was not recorded as pain"; 19% of painless group had preceding angina.
Kennedy <sup>7</sup> :			
Recent infarctions	96	8.3	4% painless, 4% showed discomfort. All postmortem material and infarcts classified as old and recent (greater or less than 8 weeks' duration).
Old infarctions	102	36.2	22.5% painless; 13.7% discomfort.
Levine and Brown <sup>8</sup>	46	48	Postmortem cases. Some histories inadequate.
Masters <sup>9</sup>	35	60	Postoperative occlusions. Narcotics and postoperative condition may have obscured pain in some cases.
Saphir <sup>11</sup>	34	38	Congestive failure, etc., might explain absence of pain in some cases.

The wide diversity of incidence of painless coronary occlusion in the series of cases of this disorder reported in the literature prompted us to study 375 cases of coronary occlusion observed in this hospital.

**Material.** We have examined all of the case histories accumulated in the past 6 years at this hospital in which coronary occlusion appears among the final diagnoses. After discarding those cases in which the diagnosis did not seem to us to be substantiated by the clinical findings, 375 cases remained. In 67 of these 375 cases the diagnosis of coronary occlusion had been recorded with a question mark, because the clinician in charge of the patient felt that there was some uncertainty as to its correctness. However, on careful examination of the histories of the cases included here, we felt that the symptomatology, physical, laboratory and electrocardiographic findings, although not pathognomonic of coronary occlusion, strongly supported that diagnosis. Of these 375 cases there were 32 (approximately 8.5%) which we classified as definitely painless. Because the great majority of patients seen in the hospital come from a distance, a relatively smaller percentage of those with coronary occlusion are seen immediately following the accident than would be the case in a hospital of similar size located in a large city. A large proportion of the patients are sent to the hospital by the family physician who is more likely to refer patients in which the

diagnosis is in doubt than cases in which it is obvious. It would seem that both of these factors would tend to make the incidence of painless coronary occlusion in our series too high rather than too low.

Our series includes cases from all the different services in the hospital, but the vast majority are from the Medical Service. Those patients admitted to other services were seen by one of the senior members of the Medical Staff. In examining the case histories of hospitalized patients, we reviewed not only the complete typewritten history taken by the intern but also the admission note made by the resident physician and the additional notes made by staff members. In the case of out-patients, the histories were taken by one of the instructors of the department, or by a senior member of the staff.

At this hospital, electrocardiograms are taken in practically all cases in which heart disease is known or thought to be present. It is probable, therefore, that comparatively few cases of coronary occlusion escaped detection because of the atypical symptomatology. In some instances, electrocardiograms taken elsewhere during the acute phases of the patient's illness were examined.

**Criteria.** All electrocardiograms were interpreted by one of the permanent staff members of the Cardiology Service. On the basis of electrocardiographic and necropsy findings, we have divided our cases of painless coronary occlusion into two groups. Group I includes 17 cases in which the autopsy findings, the electrocardiographic findings, or both, left no doubt as to the correctness of the diagnosis of myocardial infarction. The electrocardiographic abnormalities occurring in this group include significant transient *S.T.* displacement and progressive *T*-wave inversion of the coronary type, often associated with prominent *Q*-waves in the standard limb leads or similar changes in chest leads. Group II includes 15 cases in which the electrocardiograms were thought to be compatible with but not diagnostic of myocardial infarction. The electrocardiographic changes considered significant in the light of the clinical findings were *A-V* or intraventricular heart block, and abnormally prominent *Q*-waves in Lead I or in Leads II and III. We have separated these two groups so that we might base our final conclusions on the cases of Group I in which the diagnosis could be made with certainty. We have included the cases of Group II to meet the objection that too rigid electrocardiographic criteria may eliminate varieties of coronary occlusion which do not produce pathognomonic electrocardiographic changes. We realize that some of the electrocardiographic findings in this group may not have been due to myocardial infarction. Nevertheless, these findings in association with a strongly suggestive clinical history greatly support the view that the cases of this group should be regarded as highly probable examples of painless myocardial infarction. Our series of cases of painless coronary occlusion includes no instance in which the electrocardiogram was negative. It includes no instance in which there was precordial or substernal pain with or without radiation or in which the patient experienced substernal oppression, burning or constriction or precordial dis-

comfort. We also excluded from this series all cases in which there was upper abdominal pain or distress associated with cardiac dysfunction. In brief, we excluded all cases in which the diagnosis of coronary occlusion was suggested by symptoms of an "anginal" character. It has been postulated<sup>5</sup> that gradual arteriosclerotic narrowing of a coronary artery is less likely to produce pain than sudden thrombotic occlusion. If such be the case, one would expect the symptoms of painless arteriosclerotic occlusion to be less dramatic than the non-painful features of sudden myocardial infarction. Levine and Brown,<sup>8</sup> however, have shown that sudden coronary occlusion may occur without pain. Hence gradual narrowing of the coronary arteries without thrombosis is not a necessary concomitant in the painless cases. Saphir *et al.*<sup>11</sup> and Levine and Brown<sup>8</sup> have also emphasized the observation that myocardial infarction, even when associated with mural thrombi, may be present when the coronary arteries are narrowed but not completely occluded.

**Discussion.** The 17 cases placed in Group I, which includes the unquestionable examples of painless coronary occlusion, comprise 4.5% of the group of 375 cases of coronary occlusion studied. The age of the patients placed in this group ranged from 33 to 83 years. The mean age was 60.1 years. The ratio of males to females was 1.8 to 1. Twelve (71%) of this group had at one time or another a systolic blood pressure above 150 mm. of mercury, a diastolic pressure above 100 mm. of mercury, or both. In the series of 343 cases in which pain was a prominent symptom of coronary occlusion, the ratio of males to females was 3.57 to 1, but there was no other significant difference between this group and the smaller group in which coronary occlusion was painless. By electrocardiographic or necropsy evidence, 6 of the painless 17 infarctions were anterior, 9 were posterior and 2 had infarction of both anterior and posterior myocardial walls.

TABLE 2.—SYMPTOMS OF PAINLESS MYOCARDIAL INFARCTIONS.  
(BASED ON CASES OF GROUP I.)

	Cases.
Dyspnea . . . . .	8
Sudden nausea or vomiting . . . . .	5
Fainting or collapse . . . . .	4
No symptoms . . . . .	4
Vertigo . . . . .	3
Hemiparesis . . . . .	1

The incidence of the more important symptoms which occurred in the painless group (Group I) is given in Table 2. Dyspnea was the most frequent symptom and it occurred in 8 cases. Other prominent symptoms were sudden nausea and vomiting (5 cases), fainting or collapse (4 cases) and dizziness (3 cases). Hemiparesis occurred in 1 instance. In 4 cases no history of dramatic symptoms of any kind could be elicited. In some cases two or more



symptoms were present. The cases of this group are summarized in Table 3.

It will be noted that the incidence of painless myocardial infarction in our series of cases is approximately the same as in the series of cases of recent infarction reported by Kennedy.<sup>7</sup> Four per cent of his cases of recent infarction were painless. Kennedy considered the infarction as recent when the lesion indicated that it was less than 8 weeks in duration. It should be mentioned that in recent infarction the electrocardiographic changes are more likely to be pathognomonic than in infarction of much longer duration.

TABLE 3.—SUMMARY OF PAINLESS CASES OF GROUP I. (DIAGNOSIS POSITIVE.)

Patient.	Age.	Sex.	Symptoms referable to occlusion.	Blood pressure.	Location of infarct.
W. L. 389927	59	M	Sudden dizziness, ataxia, vomiting	150/94	Anterior (EKG)
E. B. 339255	83	M	Sudden dizziness, collapse	118/65	Ant. (EKG)
M. F. 348880	69	M	Gradual dyspnea	100/78	Both (EKG and P.M.)*
J. S. 352665	51	M	Progressive dyspnea, sudden dizziness and collapse	190/140	Posterior (P.M.)
I. F. 378961	65	F	No symptoms	135/72	Post. (EKG)
C. R. 393277	67	M	No symptoms	150/100	Ant. (EKG)
O. S. 393538	78	M	Sudden dyspnea	190/100	Ant. (P.M.)
D. B. 406087	80	M	Vomiting and collapse	160/77	Post. (EKG)
L. B. 130113	53	F	Progressive dyspnea	160/90	Post. (EKG)
B. O. 415029	37	M	Sudden dyspnea	245/145	Post. (EKG)
B. C. 415878	48	M	No symptoms	170/114	Post. (EKG)
W. W. 417748	47	M	Fainting, vomiting, dyspnea	105/75	Post. (EKG)
S. M. 419935	33	F	Gradual weakness, dyspnea	240/155	Both (P.M.)
E. F. 421257	54	F	Hemiparesis, vomiting	210/120	Post. (EKG)
F. V. 422726	61	F	Sudden dyspnea, cyanosis	190/90	Ant. (P.M.)
M. C. 426313	56	F	No symptoms	100/70	Ant. (EKG)
J. M. 416911	80	M	Sudden vomiting	155/100	Post. (P.M.)

\* P.M. = Postmortem examination.

It is probable, therefore, that most of the cases of myocardial infarction placed in Group I were examples of recent infarction. In many instances the lack of dramatic symptoms made it impossible to determine the age of the infarct. In comparing our series of cases with those that have been reported by others, several factors which may affect the incidence of painless coronary occlusion should be borne in mind. The more carefully the history is taken, the more frequently will painful features come to light. A patient partially narcotized because of a recent operation or because of cardiac failure would be less likely to experience pain following coronary occlusion than one who was mentally alert. We wish to emphasize that we have excluded from our painless group all cases in which "anginal" distress of any type occurred. Unfortunately, none of our patients were subjected to the Libman test of sensitivity to pain.

Typical examples of the cases included in Group I are as follows:

**Case Abstracts.** CASE 1.—W. L., No. 389927, a 59-year-old white male, dentist, was admitted, Sept. 25, 1936. Three weeks prior to admission, while working in his yard, he suddenly became very dizzy, following which he was ataxic and subsequently vomited severely for 1 hour. Three days prior to admission he had a similar attack and vomited for 6 to 8 hours. Again there was ataxia. Since then he had felt indisposed but with no

specific complaints. Throughout, there had been no abdominal pain or cardiac symptoms. Blood pressure, 150/94. Heart was not enlarged but sounds were distant.

Electrocardiogram Sept. 25 showed left axis deviation with prominent *Q*-waves in Leads I and II. There was small notched *QRS* complexes in Lead II. Repeat electrocardiogram on Oct. 12, 1936, revealed similar findings. *R*-waves were absent and *T*-waves sharply inverted in chest leads  $V_3$  and  $V_4$ . *W*-shaped complexes and sharply inverted *T*-waves were present in chest lead  $V_5$ . Repeat chest leads, Jan. 5, 1937, showed partial regression of the *T*-wave inversion.

He had another attack of severe dizziness followed by signs and symptoms of a right hemiparesis which cleared up slowly. On Jan. 5, 1937, his heart was enlarged, the blood pressure was 140/90, and there was slight ankle edema.

This patient presented positive electrocardiographic changes of anterior infarction, marked by sudden dizziness, ataxia and vomiting, but no pain.

CASE 2.—D. B., No. 406087, white male, aged 80, was admitted July 17, 1937. Three days prior to admission, on the evening following a picnic, he became nauseated and vomited once. He was seen promptly by an internist who was unable to elicit any history of pain. His pulse at that time was 42, blood pressure 160 systolic. Nausea and vomiting persisted. The morning of July 17, on arising, he suddenly collapsed but was not unconscious and experienced no pain. Examination on admission revealed a blood pressure of 88/58, pulse 32, respiration 28. He was very cyanotic. The heart was enlarged but there were no murmurs. The lung fields showed bilateral basilar râles. His pulse changed to 52 with bigeminy, later to 78 with gross irregularity. Blood pressure later was 106/72. He developed urinary retention followed by an elevation of the non-protein nitrogen. Pulse rate increased progressively to 100–120, still grossly irregular.

Electrocardiogram July 18, 1937, showed complete *A-V* block, auricular rate 86, ventricular rate 33 and elevation of the *ST* segment in Leads II and III. This tracing was repeated July 20 and on this occasion it showed auricular fibrillation with a rate of 78. There were small *QRS* groups in Lead II and large *Q*-waves. Large *Q*-waves were present in Lead III with elevation of the *ST* segment in Leads II and III. *T*-waves were inverted in Lead I only. The white blood cell count on two occasions was 15,000 and 37,000. Temperature slowly rose to 101° and later his respirations ceased. Postmortem examination was refused.

The electrocardiogram was considered diagnostic of a very recent posterior myocardial infarction. This probably occurred as a painless episode 3 days prior to admission.

The 15 cases which we have placed in Group II (the cases of probable coronary occlusion in which no pain occurred) comprise 4% of the total number of 375 cases of coronary occlusion studied. These cases are summarized in Table 4. In 5 instances there were no dramatic symptoms and the electrocardiogram was not pathognomonic. It was therefore not possible to estimate the age of the infarct if such were present. As in Group I, the sudden onset of dyspnea was the most frequent symptom, being present in 8 of the 15 cases. In this Group II, the ages ranged from 37 to 78 years with a mean age of 60.2. The ratio of males to female was 2.75 to 1. In 10 of the 15 cases (67%) there was a systolic blood pressure above 150 mm. of mercury, a diastolic blood pressure above 100 mm. of mercury or both.

TABLE 4.—SUMMARY OF PAINLESS CASES OF GROUP II (DIAGNOSIS PROBABLE.)

Patient.	Age.	Sex.	Symptoms referable to occlusion.	Blood pressure.	EKG changes.*
J. B. 325587	78	M	No symptoms	130/95	Q <sub>2</sub> , Q <sub>3</sub>
F. F. 330307	45	M	Sudden onset of nocturnal dyspnea	188/142	Compl. A-V block
E. S. 335364	58	M	Sudden dyspnea	130/90	Serial T <sub>1</sub> changes Q <sub>1</sub> present
A. vS. 353249	73	M	Sudden dyspnea	166/68	Compl. left bundle branch block
W. H. 382184	37	M	Sudden dyspnea and weakness	110/7100	Serial T <sub>1</sub> changes
A. S. 386508	77	F	Sudden severe cough	140/70	Q <sub>2</sub> , Q <sub>3</sub>
M. S. 383824	50	M	Nocturnal dyspnea	160/88	Change from normal EKG to incomp. left bundle branch block
H. F. 391447	53	M	Sudden severe weakness, fatigue, fall in blood pressure	160/120	Large Q <sub>3</sub>
A. M. 412705	65	F	No symptoms	240/140	Large Q <sub>1</sub> , Q <sub>2</sub> , Q <sub>3</sub>
C. C. 417292	71	M	Sudden dyspnea	160/110	Intravent. and A-V block changing to auric. fibrillation with intravent. block
D. A. 419998	47	M	Sudden dyspnea, weakness	150/100	Intravent. block with broad Q <sub>3</sub>
L. P. 350524	68	F	No symptoms	170/90	Partial A-V and left bundle branch block
H. J. 427418	51	M	No symptoms	114/76	Large Q <sub>2</sub> , Q <sub>3</sub> with inverted T <sub>2</sub>
C. L. 430058	71	M	Sudden dyspnea	154/90	Prominent Q <sub>2</sub> , Q <sub>3</sub> ; inverted T <sub>2</sub> , T <sub>3</sub>
F. B. 387798	59	F	No symptoms	186/98	Q <sub>2</sub> , Q <sub>3</sub>

\* Q<sub>1</sub>, Q<sub>2</sub> and Q<sub>3</sub> refer to the presence of prominent Q waves respectively in standard limb Leads I, II or III T wave changes are similarly designated.

Typical examples of the cases included in this group are as follows:

**Case Abstracts.** CASE 3.—F. F., No. 330307, aged 45, white male, was admitted Feb. 15, 1934, complaining of shortness of breath. In 1919, he developed dyspnea and was told he had a leakage of the heart. Later he was completely asymptomatic until June, 1933, when he developed paroxysmal nocturnal dyspnea and ease of fatigue, becoming progressively worse. In November he developed edema and ascites and was put to bed for 2 weeks with improvement. Four weeks prior to admission he experienced recurrence of dyspnea and edema.

Examination showed cyanosis and Cheyne-Stokes respirations. There were moist râles throughout both lung fields with enlargement of the heart, and a regular rate of 44 per minute. Blood pressure 188/142. There was ascites and some liver enlargement. Electrocardiogram of Feb. 15 showed complete A-V heart block with abnormal ventricular complex; auricular rate 97, ventricular rate 53. He was digitalized.

On the evening of his fourth hospital day he complained of pain under the upper part of the sternum, radiating into the neck. Later he cried out with a very sharp severe pain under the sternum and died a few minutes later. Autopsy was not obtained.

Presumably this was a case of painless infarction resulting in A-V heart block, and a terminal painful occlusion.

CASE 4.—No. 335364, white male, aged 58, was admitted May 7, 1934. There were no cardiac symptoms until 2½ months prior to admission when he suddenly experienced intense shortness of breath for a few minutes. He walked upstairs and collapsed; his brother, a physician, noticed that he was quite pale, covered with a cold perspiration, and pulseless. On auscultation the heart beat was quite faint. Systolic blood pressure was 110 to 112 mm. Hg ½ hour later. He had no pain. The next day he felt entirely well, although his temperature rose to 99.5° to 100.5° for several days. Prior to the attack his systolic blood pressure had been 126 to 128 mm. Hg. Subsequently he felt well.

Examination was negative. Blood pressure 130/90. Serial electrocardiograms provided by the local physician showed *T*-wave changes in Lead I and a small *Q*-wave in Lead I which were suspicious but not diagnostic of infarction. Chest leads on May 7 were negative.

The clinical history was that of coronary occlusion supported by an electrocardiogram which was compatible but not diagnostic. There was no pain.

**Conclusions.** 1. In a study of 375 cases of myocardial infarction in which the diagnosis was based on the clinical features, electrocardiographic findings, and available necropsy material, there were 17 instances (4.5%) of undoubted coronary occlusion in which no pain, substernal pressure, or other "anginal" symptoms had occurred at any time.

2. There were 15 additional cases (4%) in which there had been no pain or anginal symptoms and in which the presence of myocardial infarction was strongly suspected even though the electrocardiographic findings were not pathognomonic. In our opinion painless coronary occlusion is, therefore, relatively uncommon.

3. Among the symptoms which occurred at the time of the accident in the group of 17 undoubted cases, the most common were dyspnea, nausea and vomiting, dizziness and fainting or collapse.

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## THE ETIOLOGY OF IDIOPATHIC PNEUMOTHORAX.

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In the older literature spontaneous pneumothorax was described as invariably caused by rupture of a tuberculous focus or some other destructive process of the lung into the pleural cavity. More recently, however, it was noted that the lungs after reëxpansion may be entirely free of demonstrable disease in many of these cases. They were designated as "idiopathic pneumothorax." Kjaergaard,<sup>5</sup>

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who proposed the term "pneumothorax simplex" (1932) for those cases of pneumothorax in which no apparent cause could be recognized, gave as etiologic factors rupture of blebs near a pulmonary scar, or of an emphysematous bleb. In some of his cases, a bleb at the surface of the lung could be diagnosed by Roentgen ray films, but in the majority no blebs could be demonstrated. Castex and Mazzei<sup>1</sup> reported 12 cases of spontaneous pneumothorax in which the rupture of bullæ appeared to be the cause. In 3 of these, pleural blebs were demonstrable. The writers state that all patients were males, 22 to 30 years of age. Gordon<sup>2</sup> reported 5 cases referable to emphysematous or other blebs which were demonstrable on the films.

The presence of emphysematous and other blebs of the pleura is now thought to be the cause for the occurrence of idiopathic pneumothorax. Kirshner,<sup>4</sup> however, in 1938 has called attention to the fact that the disease will "occur in young people who rarely show emphysema and spare the aged in whom emphysema is fairly common." He also advanced evidence that idiopathic pneumothorax may be the result of "a congenital pleural defect or an acquired pleural defect with a congenital anlage," and that the formation of pleural blebs may be a secondary manifestation of a primarily weakened pleura. The cases reported below invite similar speculations in support of Kirshner's conception and strongly suggest that in the idiopathic form of spontaneous pneumothorax we are dealing with a primary constitutional inferiority of the pleural structure.

**Case Abstracts.\*** CASE 1.—Patient was admitted on May 15, 1936, having had for 10 days dyspnea and dull pain in the left axilla and below the sternum. The symptoms gradually decreased in intensity, and on admission patient was practically symptom-free. The past and family histories were irrelevant. There was no contact with tuberculosis. The physical examination was not remarkable except for the findings in the chest. The right lung was normal, but on the left expansion was decreased, the vocal sounds were metallic, there was hyperresonance and the breath sounds were barely audible. There were no râles. The heart was normal as to the position, size, sounds and rhythm, the blood pressure 130/90. Roentgen ray showed complete collapse of the left lung with no fluid or adhesions, and the mediastinum in the middle. Blood and urine showed no abnormality. The sputum was negative for tubercle bacilli. The EKG showed only respiratory arrhythmia. The tuberculin test was positive 1 to 10,000. Patient was afebrile throughout. The left lung gradually reexpanded within 75 days and was then clear on physical and Roentgen ray examinations.

CASE 2.—This patient developed sudden pain throughout his right chest and dyspnea when he was running to catch a street car. On the following day, Sept. 18, 1939, he was admitted, 20 hours after the onset of symptoms. Family and past histories were not remarkable. There was no contact with tuberculosis. The physical examination was normal except for the findings in the chest. On the right side which was hyper-

\* Cases 1 to 4 were studied at the Rhode Island Hospital; Cases 5 to 6 by Dr. J. J. Dumphy, and at the St. Vincent Hospital; Cases 7 to 9 at the Rutland State Sanatorium.

resonant, expansion, vocal fremitus, breath sounds and râles were absent. The left lung was normal. The heart was normal except for a soft systolic murmur at the apex, the blood pressure was 90/65. Roentgen ray revealed a normal left lung field and complete collapse of the right lung, with no fluid or adhesions, and the trachea was in the midline. Blood and urine were normal except for a leukocytosis of 12,850 (normal differential count) on admission. The scanty sputum was negative for tubercle bacilli. The tuberculin test was positive 1 to 1000. Electrocardiogram showed right axis deviation on the day of admission, but a normal axis on later tracings. Patient was soon afebrile and symptom-free. Reexpansion took place within 41 days after which both lungs remained clear.

CASE 3.—Patient had been in good health until 2 months ago when he had pain in the left anterior chest for 24 hours. Six weeks later he fell on his back but suffered no apparent injury. In the morning of the day of admission he experienced a sudden pain over the whole chest and particularly the precordium, radiating into back and left shoulder, but worked until the afternoon when he became pale and breathless. On admission, June 27, 1936, he was evidently in shock. Physical examination revealed absence of vocal fremitus and breath sounds with hyperresonance over the upper, and dullness over the lower, halves on the left. The heart was pushed to the right, and there was a systolic murmur at the apex. Films revealed complete collapse of the left lung with a fluid level at the fourth rib and heart and mediastinum displaced into the right side. The EKG showed a slight depression of  $ST_2$ . An exploratory aspiration on the left revealed pure blood. Pulse and blood pressure could barely be registered. Patient remained in shock and died 6 hours after admission.

*Autopsy* (Dr. Egoville). When the left pleural cavity was opened, air escaped under positive pressure. The left pleural cavity contained about 3000 cc. of liquid blood and a few clots. The left lung was completely collapsed. The right pleural cavity contained no blood, and the lung was free of adhesions. The mediastinum was pushed to the right so that the apex of the heart rested beneath the sternum. There was no free blood in the mediastinum. The heart was normal. At the apex of the collapsed left lung there was slight scarring and a few emphysematous bullæ, but the pleural surface was everywhere intact. No bleeding point was discovered. The cut surface was elastic and retractile. The pulmonary arteries showed no abnormality. The right lung showed also a slight amount of apical scarring but was not otherwise remarkable.

CASE 4.—Patient was admitted on March 30, 1936, with complaints of stabbing pain in the left chest and dyspnea on exertion of 'about 2 months' duration. He could not recall any injury. The family and past histories were negative. Heart and electrocardiogram were normal; blood pressure 116/78. However, expansion, vocal fremitus and breath sound over the left hemithorax were diminished and there were dullness and a succussion splash at the base with hyperresonance above. The findings over the right hemithorax were normal. Roentgen rays showed considerable collapse of the left lung, with fluid covering the diaphragmatic dome and some shifting of the mediastinum to the right. There was a leukocytosis of 14,500, and 10,200 after 5 days (normal differential count). Otherwise blood and urine were normal. During the first 3 days the fluid increased, was aspirated and did not recur. The specimen was straw-colored and sterile on culture and guinea-pig inoculation. Patient remained well and was discharged after 23 days of hospitalization, still with a partial pneumothorax. His left lung reexpanded within the following 2 months, and his chest was then entirely clear.

CASE 5.—Five hours before admission, Feb. 15, 1938, patient was suddenly seized by severe pain in the right chest and shoulder, and dyspnea,

when driving a car. The family history was negative. He had scarlet fever and 2 pneumonias in childhood and an appendectomy 5 years ago. The essential features of the physical examinations were confined to the chest; the heart revealed normal rhythm, size and sounds; the blood pressure was 102/64. The right hemithorax showed restricted expansion, absent vocal fremitus and breath sounds, and hyperresonance on percussion. The left side was normal. On Roentgen ray there was complete collapse of the right lung which was seen as a round small shadow in the region of the right hilus and no fluid. The left lung was normal. Blood and urine were normal except for an initial leukocytosis of 11,300 (normal differential count). The sputum was persistently negative for tubercle bacilli. Patient was afebrile throughout and symptom-free from the third day. His right lung reexpanded within about 1 month, after which there was no evidence of pulmonary disease. He has occasionally been seen later on and remained in good health.

CASE 6.—This patient, seen on Oct. 4, 1934, complained of a dull ache in the left chest and dyspnea. These symptoms had suddenly started shortly ago when patient was blowing a trumpet. He was little concerned because he had experienced similar attacks twice within the previous 2 years, once on strain during defecation and once on inflating a toy balloon. Each time he became symptom-free within 1 week. The family history was negative. He had influenza in 1918 and a tonsillar abscess in 1930. The size, rhythm, and sounds of the heart were normal; blood pressure 140/80 on the first day and 120/80 later on. There were hyperresonance and absent vocal fremitus and breath sounds on the left, and normal findings on the right. On Roentgen ray there was about 50% collapse of the left lung, evenly distributed, and no fluid or adhesions. Blood and urine were normal. Patient was afebrile throughout and became symptom-free within 1 week. Full reexpansion of his left lung was noted 28 days after onset. The lung fields were then clear and patient remained well.

CASE 7.—Patient had always been in good health, except for frequent colds in the past two winters, the last one early in January, 1935. Otherwise the family and past histories were negative. On Jan. 23, 1935, he experienced blood-stained vomiting, and a sudden sharp pain in the right chest, followed by dyspnea. Diagnosed as having a duodenal ulcer, he responded to ulcer diet elsewhere. Simultaneously he had suffered almost complete spontaneous pneumothorax on the right without effusion. On admission, Mar. 26, 1935, physical examination revealed no remarkable findings except in the chest: There were hyperresonance and absence of breath sounds over the upper parts of the right hemithorax. The lower half of this side, the left lung, heart and blood pressure were normal. Roentgen ray revealed a small residual pneumothorax at the right top. Otherwise the lung fields appeared clear on both sides except for accentuated hilus markings. Blood and urine were normal except for a leukocytosis of 12,500 (normal differential count). Daily sputum examinations were negative for tubercle bacilli. Patient was afebrile and symptom-free throughout. His right lung reexpanded within 5 months and remained clear.

CASE 8.—Patient had been in excellent health until a month before admission, when, without recognizable reason, he suffered a right spontaneous pneumothorax with sharp pain in the chest and dyspnea for 2 days. His mother had died of tuberculosis when he was 5 years old. Physical examination revealed expansion, vocal fremitus, and breath sounds diminished and the percussion note hyperresonant, over the right hemithorax. The left hemithorax and the heart were normal; blood pressure 118/70. Roentgen ray revealed a residual collapse on the right, about 30% in extent, evenly distributed, with no adhesions or fluid. The left lung field was clear.

Blood and urine were normal. No sputum could be obtained. Fifty-two days after admission, *i. e.*, about  $2\frac{1}{2}$  months after onset, the right lung had fully reexpanded. Patient was transferred to another sanatorium and observed at yearly intervals. His lungs remained always clear.

CASE 9.—This young man is a waiter in the physicians' dining room of the institution since February, 1939. His family and past histories, physical examination, and Roentgen rays had been found negative. On Aug. 23, 1939, after playing baseball and taking a cold shower, he experienced sudden onset of pain in the right chest and dyspnea. He was immediately admitted as a patient. Physical examination revealed the cardinal signs of pneumothorax on the right. The left lung, heart, and blood pressure were normal. Roentgen rays showed about 50% of collapse of the right lung, evenly distributed, without fluid or adhesions. The left lung was clear. Blood and urine were normal, and sputum was not obtained. On the basis of the characteristic findings as discussed later, a diagnosis of idiopathic pneumothorax was made. Patient was symptom-free on the following day and permitted to resume work with his right lung still collapsed. It reexpanded within 30 days. Patient is now in good health (November, 1939) and his chest films show no evidence of disease.

TABLE 1.—DATA ON THE 9 CASES.

Case No.	Initials.	Color.	Occupation.	Side.	Age.	Sex.	Adhesions.	Fluid.	Occurrence.	Duration of re-expansion, in days.
1	C. N.	White	Fruit peddler	Left	21	Male	No	No	1	80
2	J. H.	White	Unemployed	Right	20	Male	No	No	1	40
3	G. L.	White	Messenger	Left	34	Male	No	Blood	1	Died.
4	E. A.	White	Packer	Left	40	Male	?	Yes	1	120+
5	W. D.	White	Salesman	Right	46	Male	No	No	1	30
6	F. G.	White	Dress attendant	Right	26	Male	No	No	3	30
7	F. H.	White	Electrician	Right	31	Male	No	No	1	150
8	J. S.	White	Cook	Right	23	Male	No	No	1	70
9	J. B.	White	Waiter	Right	20	Male	No	No	1	30

**Discussion.** All of the preceding cases suffered one or more attacks of spontaneous pneumothorax precipitated by petty causes or no evident causes at all. Case 3 terminated fatally by hemopneumothorax. The other 8 patients were clinically well after the collapsed lung had reexpanded, and no tuberculosis or any other lesion within the lung parenchyma could be demonstrated. The age incidence is striking. None of the 9 patients was beyond 46, 7 were below 35, 4 below 25. The age average is 29. Similar observations were made by Kirshner as well as Mazzei and Castex. This obvious incidence of the disease among the young should exclude pulmonary emphysema as an etiologic factor. Emphysema is a disease of older life, and will rarely cause collapse of the affected lung. Furthermore, in reviewing the literature, one is impressed by the tremendous predominance of the disease in the male sex. Its occurrence in



women may indeed be considered as an exception. All our 9 cases were males. Age and sex incidence thus suggest a constitutional factor.

It has been observed that in the majority of cases complete collapse is the rule. This is explained by the obvious absence of adhesions between the parietal and visceral pleural leaves. It is indeed surprising that one should not more frequently encounter pleural adhesions which might have been produced by previous incidental infections, tuberculous first infections, or simply protective reactions preliminary to the present perforation of the pleura, whatever its cause may be. At least 8 of our 9 cases showed complete collapse of the affected lung, and no adhesions were demonstrable. The one remaining case (Case 4) which came to observation several weeks after onset, showed a considerable degree of reëxpansion, thus making it impossible to decide whether adhesions had been present or not. This is the same case in which fluid had developed within the pleural cavity, and it is in this point that this case again distinguishes itself from the others in which absence of adhesions and fluid are the predominant features. The one case which terminated by hemo-pneumothorax cannot be considered from this angle. We would expect that the mechanical insult of a pleural perforation and sudden collapse of the lung would normally be answered by the production of an effusion, even without the factor of pleural infection. The fact that in the majority of our cases evidence of effusion remained entirely wanting, again suggests functional impairment of the pleura.

Considering the sluggishness of the pleural response, it is not surprising that repeated collapse of the same lung should be encountered. Such cases are frequently met with in the literature. Watson and Robertson<sup>8</sup> reported 3 cases of recurrent spontaneous collapse of the lung. Case 6 of our series presents a typical example. It is a well known fact that in collapse of the lung, spontaneous or artificial, the pleural leaves tend to become adherent to each other after reëxpansion has taken place. Yet this does not seem to be so in cases of idiopathic pneumothorax. Idiopathic pneumothorax is thus apt to appear in the form of recurrent pneumothorax.

A major argument in favor of idiopathic pneumothorax as a constitutional disease is derived from the observation of familial occurrence. Larsen<sup>6</sup> mentions spontaneous collapse in two brothers who were apparently well otherwise. Willis<sup>9</sup> reports on 2 cases, and Götzsche<sup>3</sup> on 5 cases of idiopathic pneumothorax within the same family. In our series we have not had the opportunity of registering a case of familial pneumothorax. LeWald<sup>7</sup> and Larsen<sup>6</sup> commented on the duration of time required for the collapsed lung to reëxpand and found it to be unduly long, ranging from 6 to over 12 months. Normally, in the absence of manifest pulmonary dis-

ease or pleural effusion, we would expect the affected lung to re-expand in about 4 to 8 weeks. Persisting perforation can be dismissed in the face of partial and gradual reëxpansion. There is reason to suspect a functionally inadequate rate of absorption for air of the pleura in the cases under consideration. LeWald bases his observations on 2 and Larsen on 7 cases. In the average of our cases, however, reëxpansion was usually accomplished within or slightly beyond 2 months.

**Summary and Conclusion.** The etiology of idiopathic pneumothorax is brought into relation with the following factors:

1. Age incidence, usually below 40.
2. Sex distribution, practically always male.
3. Adhesions, usually absent.
4. Fluid, usually absent.
5. Frequently recurrent pneumothorax.
6. Familial occurrence.
7. Possibly slow reëxpansion rate.

Emphysema should be dismissed as an etiologic factor in idiopathic pneumothorax. Individual blebs of the pleura may be present. If so, they are likely to be caused by traction on a primarily weakened pleura as suggested by Kirshner and in the light of the presented evidence. The primary cause of the idiopathic pneumothorax is to be sought in a constitutional inferiority of the pleural structure.

The author is indebted to Dr. Frank T. Fulton of Providence, R. I., Dr. John J. Dumphy of Worcester, Mass., and Dr. Ernest B. Emerson, of Rutland, Mass., for their valuable coöperation.

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## HEMOPTYSIS AND PULMONARY ARTERIAL RUPTURE.\*

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In the present communication are reported certain observations concerning the frequently ruptured branch of the pulmonary artery, which appears to be the source of fatal hemoptysis.

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**Material.** Between 1934 and 1939, 246 cases of pulmonary tuberculosis, some of which had anthracosilicosis, came to necropsy at the Laboratory of Pathology of the White Haven Sanatorium. Of this number, 12 died of massive hemoptysis. The study is based upon the clinical, pathologic and postmortem roentgenologic observations of these cases.

**Method.** In every case a postmortem roentgenogram of the chest was made before the necropsy. The lungs and heart were removed in one mass. Through a catheter inserted into the conus arteriosus, 300 to 400 cc. of 50% barium sulphate suspended in water were injected into the pulmonary arterial system. A ligature was tied around the conus arteriosus to prevent a possible back-flow of the barium into the heart. After the arteries were injected, air was pumped into the bronchial tree in order to inflate the lungs, particularly the cavities. Then the specimen was laid on a cassette containing an ordinary Roentgen film and an exposure was made using these factors: 100 prereading kilovolts, 75 milliamperes, 5/20 second exposure time and a distance of 4 feet. In 3 cases the pulmonary arteries were injected using the same amount of barium, but with the lungs *in situ*. This procedure was accomplished by inserting a catheter into the conus arteriosus through an incision made on the right ventricle. A ligature was tied around the conus arteriosus. In order to expose the right ventricle for the above procedure small segments of the 3d, 4th and 5th costal cartilages were removed just lateral to the left border of the sternum. Having injected the arteries, the subject was tied to the cassette changer with the back toward the tube and stereoscopic plates were exposed, using the following factors: 150 prereading kilovolts, 75 milliamperes and 5/20 second exposure time at a distance of 5 feet.

**Findings.** (See Table 1.) Of the 12 cases studied, the ruptured vessel was discovered in 10. In 2, although the ruptured vessel could not be definitely identified, it was reasonably certain that it was in the cavity in the upper lobe which contained blood clots. In 6, the ruptured vessel was on the right side and in 4, on the left. In 10 the source of hemorrhage was in the upper lobe and in 2 in the lower lobe. In all the ruptured artery was located within a cavity and the point of rupture was on the medial aspect of the cavity. In 5, the ruptured vessel assumed the shape of so-called Rasmussen's aneurysm. In all the source of hemorrhage was the perforation of the blind pouch of the pulmonary artery embedded in the medial part of the cavity wall. In none was the hemorrhage the result of a break of a cord-like structure so often found crossing the tuberculous cavity. In all the tuberculosis was chronic with considerable fibrosis. Pulmonary fibrosis was particularly marked in 5 cases in which there was anthracosilicosis as well as tuberculosis. In 11 the fatal hemoptysis occurred while the patients were in bed. In 1, it came while walking.

The postmortem arteriograms (Figs. 1 and 2) showed that the most frequently involved artery in the series studied was the first branch of the pulmonary artery which extended upward into the upper portion of the upper lobe. The arteriograms of the cases with the lungs *in situ* (Fig. 3) showed that the first branch of the pulmonary artery lies approximately at the level of the second costal cartilage slightly medial to the parasternal line. The cord-like

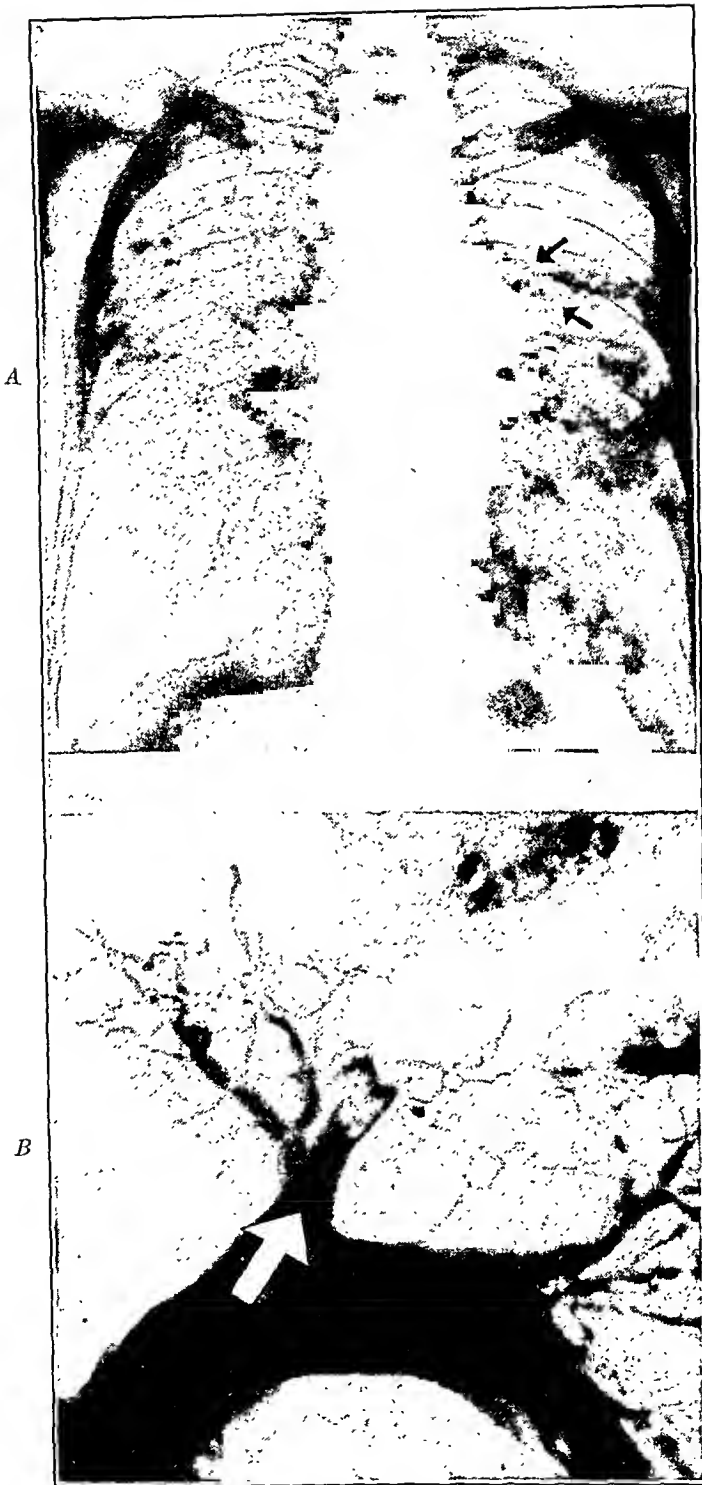


FIG. 1A.—Case 9. In the left upper lobe is a large cavity. Arrows indicate lower border of cavity at second intercostal space anteriorly.

FIG. 1B.—Same case. Arrow indicates first branch of pulmonary artery and its point of rupture.

A



B



FIG. 2A.—Case 10. Arrows indicate lower border of cavity at second rib anteriorly.  
FIG. 2B.—Same case. Arrow indicates aneurysmal dilatation of stump of first branch of pulmonary artery and its point of rupture.

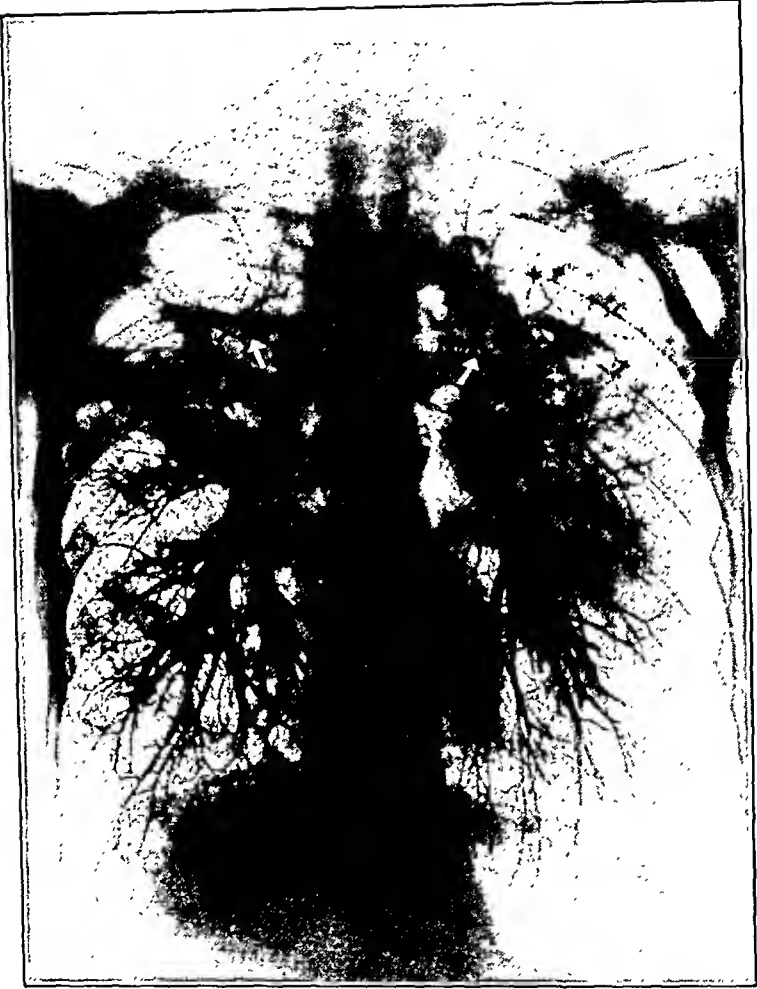


FIG. 3.—Pulmonary arteriogram with lungs *in situ*. Arrows indicate first main branch of pulmonary artery on either side, and level at which it comes off main artery.

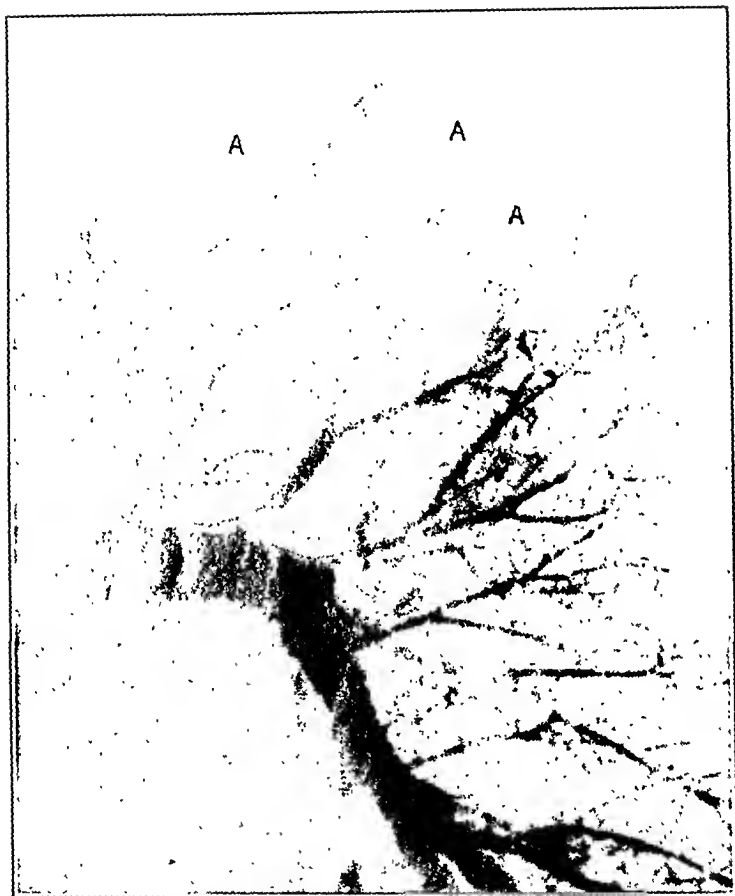


FIG. 4.—When cavities (A) are small and are located in periphery of lung, only arterioles are destroyed. When hemoptysis occurs in such a case it is probably never massive.

structures crossing the cavities very rarely contained blood-vessels, and when they did the vessels were very much narrowed on account of panarteritis and thrombosis.

TABLE 1.—CLINICAL AND PATHOLOGIC DATA.

Case No.	Necropsy No.	Age.	Sex.	Type of pulmonary tuberculosis.	Side of involvement.	Brief description of ruptured vessel.
1	244	42	M	Chr. fibroulcerative	Right	Rasmussen aneurysm found in rt. lower lobe cavity.
2	258	22	M	Chr. fibroulcerative	Right	Cavity in rt. upper lobe contained blood clots. Bleeding vessel not found.
3	261	48	M	Chr. fibroulcerative with anthracosilicosis	Left	Cavity in lt. upper lobe showed rupt. branch of pul. art.
4	279	28	M	Chr. fibroulcerative	?	Rupt. vessel not demonstr.
5	282	39	M	Chr. fibroulcerative and siderosis	Left	Cavity near sternal border of lt. upper lobe showed Rasmussen aneurysm.
6	286	51	M	Chr. fibroulcerative with anthracosilicosis	Right	Cavity in rt. upper lobe showed Rasmussen aneurysm.
7	340	29	M	Chr. fibroulcerative with anthracosilicosis	Right	Cavities in rt. upper lobe contained clots. Rupt. vessel demonstr. by arteriogram.
8	388	63	F	Chr. fibroulcerative	Left	Rupt. vessel demonstr. in lt. upper lobe by arteriogram.
9	389	52	M	Chr. fibroulcerative	Left	Rupt. vessel demonstr. in lt. upper lobe by arteriogram.
10	413	55	F	Chr. fibroulcerative	Right	Rupt. vessel demonstr. in rt. upper lobe by arteriogram.
11	448	53	M	Chr. fibroulcerative with anthracosilicosis	Right	2 perf. vessels in bottom of large cavity in rt. upper lobe.
12	458	34	M	Chr. fibroulcerative	Left	Rasmussen aneurysm in upper part of lower lobe.

**Discussion.** Evidently there are two outstanding reasons why the first branch of the pulmonary artery is most often involved in fatal hemoptysis in pulmonary tuberculosis as found in our series. The first is that in pulmonary tuberculosis of the adult type with the disease predominantly in the upper lobe, it is the first branch of the pulmonary artery supplying the apex that bears the brunt of the pathologic processes. The arterial changes vary, depending on the anatomic distribution of the morbid process and the form of tuberculosis, whether chronic or acute. In the chronic form, when the disease was localized in the peripheral zone of the upper lobe with considerable fibrous tissue infiltration about the diseased area, the pulmonary artery within the fibrotic areas becomes sclerosed and its lumen almost obliterated, while the pulmonary artery



outside the fibrotic zone remains practically normal in caliber. In some cases there is actual dilatation of the artery suggesting an attempt on the part of the heart to force blood into the artery encased within the fibrotic zone. When the disease is acute with widespread consolidation, the artery is universally narrowed throughout the entire consolidated area. Widespread thrombosis in such an artery is often encountered when studied histologically. Regardless of the type of the vascular change, the important point is that in pulmonary tuberculosis, it is the first branch of the pulmonary artery which is most frequently destroyed.

The second reason that the first branch of the pulmonary artery is a frequent source of fatal hemorrhage is that tuberculous cavities begin, as a rule, in the apex of the upper lobe, and as they become larger, the peripheral ends of the first branch of the pulmonary artery become eroded. The arteriography showed that when a cavity is in the extreme apex of the upper lobe, its dimension not larger than an inch, and its lower border not as low as the second rib, only the second and third orders of this branch are eroded by the cavitation (Fig. 4). It is doubtful that when vessels of small caliber are eroded a fatal hemorrhage can ever occur. However, as the cavity increases in size, the time may come when it encroaches at right angles upon the main trunk of the first branch of the pulmonary artery. At this stage a fatal hemorrhage becomes a definite possibility.

Because the first main branch of the pulmonary artery was often involved in fatal hemoptysis, attempts were made to determine its topographic anatomy in relation to the usual chest roentgenogram. This study showed that this main branch comes off the main artery at about the second costal cartilage, slightly medial to the parasternal line. In all our cases the cavity was large and extended down to the level of the second rib or second intercostal space close to the sternum. This fact may have a clinical significance in that any tuberculous cavity in this location may be regarded dangerous, particularly as a possible cause of fatal hemorrhage.

In all the cases the tuberculosis was chronic in form. We have not seen a case of fatal hemoptysis in acute tuberculous pneumonia. The reason for this is easy to understand. The arteriograms made on the cases of tuberculous pneumonia showed very little erosion of the pulmonary vascular tree. When the cavities form, they are, as a rule, small and are located in the periphery of the lungs, where only the smaller branches of the pulmonary artery are involved.

In regard to the pathogenesis of arterial rupture in pulmonary tuberculosis there appears to be much controversy. Auerbach<sup>1</sup> reviewed this question. Some of the observations concerning the mechanism of arterial rupture in pulmonary tuberculosis are as follows: Invasion of the adventitia and media of the pulmonary

artery by granulation tissue leaving the intima and the "white blood clot" within the lumen as the only wall separating the vessels from the cavity (Meyer<sup>8</sup>), hyaline degeneration of the blood-vessels due to nutritional disturbances resulting in tissue necrosis (Eppinger<sup>4</sup>), gradual erosion of the blood-vessel by tubercle bacilli (Letulle<sup>7</sup>), gradual dilatation of the blood-vessel due to the destruction of the elastic tissue (Bogen<sup>2</sup>), and active destruction of the blood-vessels by the tuberculous process (Jaffe<sup>6</sup>).

The incidence of fatal hemoptysis in pulmonary tuberculosis is reported variously as 1% (Wolff<sup>9</sup>), 4% (Auerbach<sup>1</sup>) and 6.8% (Fishberg<sup>5</sup>). The 12 out of 246 cases we studied makes the incidence in our series 5%. It is possible this incidence may be reduced if tuberculous cavities occurring in the region of the first branch of the pulmonary artery are collapsed. The cavity walls will then be approximated, thus providing protection to the eroded ends of the pulmonary artery. Furthermore, vascular sclerosis seems to occur more frequently in a tuberculous lung, when it is under collapse.<sup>3</sup> Such sclerosis, if brought about, may aid in preventing aneurysmal dilatation and subsequent rupture of the diseased artery, thereby preventing fatal hemoptysis.

**Summary and Conclusions.** 1. Twelve cases of fatal hemoptysis in pulmonary tuberculosis were studied clinically, pathologically and by postmortem pulmonary arteriography.

2. In every case the tuberculosis was chronic with considerable fibrosis.

3. The incidence of fatal hemoptysis in our series was 5%.

4. The method of performing postmortem pulmonary arteriography is described in detail.

5. Of the 12 cases, the ruptured pulmonary artery was found in 10. In 8 the ruptured vessel was the first main branch of the pulmonary artery, which lies at the level of the second costal cartilage slightly medial to the parasternal line.

6. A cavity reaching the second costal cartilage may be considered dangerous as far as possible erosion of the first main branch is concerned. Hence it may be well to consider collapsing such a cavity with a view to reducing the incidence of fatal hemorrhage.

The authors are greatly indebted to Dr. Joseph Walsh for his suggestions and permission to use the necropsy material of the White Haven Sanatorium. The members of the Medical Staff of the Sanatorium were kind in giving us clinical data on these cases.

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## NEGATIVE RESULTS OF IRRADIATION THERAPY OF THE PYLORUS AND BRUNNER'S GLAND AREA IN PATIENTS WITH POLYCYTHEMIA VERA.

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IRRADIATION therapy has had various methods of application in the treatment of polycythemia vera. Harrop and Wintrobe<sup>2</sup> have provided an excellent review of this topic.

Within recent years, Morris<sup>6</sup> and Hitzenger<sup>3</sup> have advanced the interesting hypothesis that in polycythemia vera the overproduction of erythrocytes is due to an excessive elaboration of the anti-pernicious anemia principle (intrinsic factor of Castle), a condition which finds its antithesis in pernicious anemia in which the formation of this hemopoietic factor is inhibited. Singer<sup>7</sup> carried the hypothesis a step further by performing a gastrectomy on a patient with polycythemia who was also suffering from a duodenal ulcer. One year following the operation the patient's erythrocyte count was 4.6 million.

Hitzenger<sup>3</sup> in 1934 in an attempt to reduce the hypothetical excess of intrinsic factor irradiated the stomach of 2 of his patients with the result that temporary benefit was obtained. In one case the hemoglobin fell from 140% to 100% and red blood count from 8.9 million to 5.6 million per c.mm. In the second case the hemoglobin was reduced from 128% to 110%, and the red blood count from 9.5 to 7 million. However, the duration of the remission persisted only for a few months. He was inclined to feel that the Roentgen ray doses were too small. A different technique was employed in one case by Andersen, Geill, and Samuelson<sup>1</sup> in 1938. They confined the irradiation to the pylorus and upper duodenal region, since Meulengracht's<sup>5</sup> studies suggested that the pyloric and Brunner's glands were the site of elaboration of the intrinsic factor. With repeated treatments over a period of 4 months the red blood count gradually fell from 134% to 100% (Sahli). The color index increased from 0.61 to 1.20. The red blood cells declined in number from 11 million to 4.1 million per c.mm., and the mean red cell diameter increased from 7.29 to 7.81. Following the course

of treatment the patient showed clinical improvement and the red color of the face and hands diminished.

In view of the satisfactory results reported by Andersen and his co-workers, we undertook to repeat their experiments both from the viewpoint of treatment and to obtain further evidence for or against the hypothesis that polycythemia vera may be due to an excess of the hematopoietic factor.

**Methods of Study.** Four cases of polycythemia vera were studied. They were all classical cases. There were 3 males and 1 female. Blood studies were carried out just prior to, during, and for varying periods after the completion of the Roentgen treatments. The hemoglobin determinations were made with a Sheard and Sanford photometer.\* The erythrocyte counts were made in the routine manner. The hematocrit values were estimated with Wintrobe hematocrit tubes. The Congo Red method described by Keith, Rowntree and Geraghty<sup>4</sup> was employed in the evaluation of the plasma and total blood volumes.

In this study we have followed the Roentgen ray technique outlined by Andersen, Geill, and Samuelson.<sup>1</sup> Their method is as follows: The patient drinks a small portion of contrast media and is immediately placed in a recumbent position on a fluoroscopic table. In a few minutes the pyloric region is visualized on the fluoroscopic screen. A metal ring 9 cm. in diameter is placed on the abdomen in such a position that the pylorus and a part of the descending duodenum is seen in the center. A circle is then drawn with indelible pencil on the skin around the metal ring. This field is later irradiated while the patient is placed in exactly the same position as during the fluoroscopic examination. Their therapy factors were: 150 kv., 5 ma., 0.5 mm. copper filter, 40 cm. focus-skin distance. We outlined the field in the same manner but used more penetrating radiation. The technique was varied to a slight extent as noted in the following, and the time distribution had to be modified somewhat to suit the patient. These variations should certainly not reduce the effectiveness of the radiation. Two hundred and 220 kv. were used with filters of 0.5 and 1 mm. copper. The half value layer amounted to 0.9 and 1.7 mm. copper respectively. The current was 30 and 15 milliamperes. At first 70 cm. focus-skin distance was used and a circular field which was increased from 9 cm. diameter to 10 cm. when no response was noted after the first few treatments. In all the treatments given after April 6, 1939, a 10 by 10 cm. square cone was used with slight compression and the focal distance was then 50 cm. A few treatments were also given from a posterior field. 200 r as measured in air was applied each time. The dates of the treatments as well as the figures obtained from the blood examinations are recorded in Tables 1 to 4. When the treatments were discontinued after about 3 months, the total number of Roentgens given amounted to 2400 r to each of 2 patients, 2200 r to 1, and 2800 r to the fourth patient. Andersen, Geill and Samuelson applied a total of 2600 r in about 4 months.

**Results.** From the analysis of the data in Tables 1 to 4 it is apparent that Roentgen therapy applied to the pylorus and duodenum was of no benefit to the polycythemia. In no instance was the blood volume appreciably reduced. (In Case 4, blood volume studies could not be carried out because of the poor condition of the patient's veins.) Similarly, no reduction in the hematocrit values

\* Central Scientific Company, Chicago, Illinois.

were obtained. While variations were noted from time to time in the erythrocyte counts and hemoglobin concentrations, no material reductions occurred during the course of, nor for an adequate period following the irradiation.

In our opinion the ineffectiveness of the treatment was not due to improper nor to inadequate application of Roentgen therapy inasmuch as we followed the technique of Andersen and his colleagues fairly closely. Moreover, we used more penetrating rays, a greater focus-skin distance, and therefore a considerably higher depth dose. The failure to obtain any therapeutic response prompted

TABLE 1.—CASE 1, L. R., ♂ 29.

Date.	Roentgen units.	Hemoglobin in % (17 gm. /100 cc. = 100%).	Erythrocytes (Mill. per c.mm.).	Hemato- crit %.	Blood volume (in liters).	
					Plasma vol.	Total vol.
1939	Anterior exposure					
2-11	200	146	8.9	86	1.45	10.32
2-14	200					
2-16	200	150	8.16	85		
2-18	200					
3-18	200	130	8.32			
3-20	200			74	2.61	10.82
3-22	200					
	Posterior exposure					
5-11	200	116	11.45	78		
5-13	200					
5-15	200			76	2.7	10.53
5-17	200					
Total	2200					
8-11		130	9.3	83	1.8	10.6

TABLE 2.—CASE 2, J. S., ♂ 48.

Date.	Roentgen units.	Hemoglobin in % (17 gm. /100 cc. = 100%).	Erythrocytes (Mill. per c.mm.).	Hemato- crit %.	Blood volume (in liters).	
					Plasma vol.	Total vol.
1939	Anterior exposure					
2-18	200	129	5.5	73	2.77	10.77
2-20	200					
2-22	200					
2-24	200	126	6.23	75	2.88	10.69
4-1	200					
4-3	200	128	7.75	72.5		
4-5	200	134	7.14			
5-3	200	135	7.0			
5-5	200					
5-8	200	133	6.0			
	Posterior exposure					
5-10	200					
5-12	200					
Total	2400					
6-2		125	8.0	76		
6-23				75	2.74	10.53

us to discontinue the treatment after about 3 months. While the evidence obtained in the present study does not lend support to the concept that polycythemia vera is the antithesis of pernicious

TABLE 3.—CASE 3, R. H., ♂ 30.

Date.	Roentgen units.	Hemoglobin in % (17 gm. /100 cc. = 100%).	Erythrocytes (Mill. per c.mm.).	Hemato- crit %.	Blood volume (in liters).	
					Plasma vol.	Total vol.
1939	Anterior exposure					
4-20	200	130	9.7	77.4		
4-21	200					
4-24	200					
4-26	200	130		77.4		
5-24	200				2.4	10.75
5-26	200	131	10.0	77.4		
6-14	200					
6-16	200	123	9.3	73.0		
	Posterior exposure					
6-19	200					
6-21	200	144		76.3		
	Anterior exposure					
7-18	200	140	9.5	75.0		
7-20	200					
7-25	200					
7-27	200					
8-17		127	10.0	77.0	3.4	12.3
Total 8-31	2800			79.0		

TABLE 4.—CASE 4, C. D., ♀ 65.

Date.	Roentgen units.	Hemoglobin in % (17 gm. /100 cc. = 100%).	Erythrocytes (Mill. per c.mm.).	Hematocrit %.
1939	Anterior exposure			
3-6	200	114	7.4	66.5
3-9	200			
3-11	200			
3-13	200	130	6.12	
4-6	200	123	6.38	
4-8	200			
4-10	200	133	6.86	
4-12	200			
5-10	200	127	7.16	
	Posterior exposure			
5-12	200			
	Anterior exposure			
5-15	200			
	Posterior exposure			
5-17	200			
Total 7-22	2400	120	8.5	72.

anemia, it is nevertheless recognized that no definite conclusions can be drawn, since it is possible that Roentgen ray even in heavy dosage may not interfere with the production of intrinsic factor.

**Conclusions.** 1. Roentgen therapy applied to the pylorus and duodenum in 4 patients having polycythemia vera failed to induce any remissions in the blood picture.

2. Roentgen therapy directed to the pylorus and duodenum appears to be of no therapeutic value in the treatment of polycythemia vera. The present study fails to confirm the observations of Andersen, Geill, and Samuelson.

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### THE USE OF INTRAVENOUS SODIUM CHLORIDE IN PYROTHERAPY.

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REACTIONS to artificial fever therapy have been greatly reduced during the past decade. This has been due to improved methods of inducing fever and to an increased knowledge of the physiologic changes that occur during exposure to excessive heat therapy. A better understanding of the indications for and contraindications to this type of therapy has also contributed toward the lessening of untoward reactions.

Various types of reactions have been reported such as nausea, vomiting, hematemesis, herpes simplex, weakness, debility, delirium, shock, hyperpyrexia, tetany and occasionally death.<sup>7,14,24,27</sup> The causes of these reactions have not always been determined, due to incomplete information concerning the physical and chemical changes that occur in patients subjected to artificial fever.

**Administration of Sodium Chloride During Artificial Fever Therapy.** Sodium chloride has long been known to exert a beneficial influence on the human organism exposed to excessive heat. Salt is now used in foundries, industrial plants and construction projects operating under conditions of extreme heat. Salt is also given to patients who are being treated by fever. It is usually administered by mouth

during the period of exposure to heat or fever, and in some instances also preceding and following it.

Increased or excessive perspiration occurring during artificial fever leads to a more or less pronounced loss of the sodium chloride.<sup>6,16,17,26</sup> In order to make up for this loss, salt must be administered. If correctly timed, the introduction of salt may prevent further excessive perspiration and critical loss of sodium chloride. One of the most important physiologic actions of sodium chloride in fever is its tendency to cause hydremia<sup>12,18</sup> and to effect a favorable shift in water balance. We do not wish to enter here into a detailed discussion of sodium chloride metabolism. Suffice it to mention that salt has many complex relations to water exchange, osmotic equilibrium and body chemistry.<sup>2,4,15,21</sup>

Salt is usually administered in a 0.3 to 3% solution. The use of salt in capsules and tablets or in the form of foods high in content of sodium chloride has also been reported. The literature attests to the beneficial subjective and objective effects observed. Increased tolerance to heat and decreased weakness and debility have been reported most frequently.<sup>11,15,19</sup> A type of heat exhaustion known as stokers' cramps has been studied and seems to be due to excessive chloride loss.<sup>25</sup> It was shown that the incidence of sunstroke among laborers exposed to high temperatures during the building of Boulder Dam could be materially lessened by the administration of sodium chloride.

**Nausea and Vomiting During Artificial Fever.** During the past 5 years we have treated more than 500 patients with artificial fever, using the blanket method. Therapeutic results have been satisfactory and there have been few serious reactions.<sup>8a,b</sup>

Despite the oral administration of various concentrations of salt solutions, nausea and vomiting were observed in 60% of our patients. Patients undergoing pyrotherapy are not permitted to have breakfast, as this predisposes to vomiting. Since they do not eat lunch during the treatment, prolonged vomiting becomes of serious import. Not only is this reaction undesirable because of subjective discomfort, but patients who can otherwise be ambulatory lose one to several days of work, thus causing financial loss and necessitating rearrangement of working hours.

In reading over the literature, we have been unable to find mention of remedies effective in preventing this nausea and vomiting. Of the few procedures suggested, none seemed to be rational and none had been tried under exact clinical conditions permitting evaluation.

**Effects of Various Methods of Administration of Salt.** The following methods of administration of sodium chloride were studied:

*Sodium chloride by mouth in tablet or capsule form preceding, during and between pyrotherapy treatments:* This method of administering salt was found to be unsatisfactory because salt in this



concentrated form, even though enteric coated tablets were used, may lead to gastric and intestinal irritation resulting in nausea, vomiting and diarrhea.<sup>3</sup> The rapid excretion of salt by the kidneys made it doubtful that salt may be stored by preliminary administration.<sup>23</sup> Further, many ambulatory patients did not take the salt at the regular intervals of time prescribed.

*Salt solutions by mouth during pyrotherapy:* Salt solutions by mouth are not entirely satisfactory because of their disagreeable taste. Many patients are so drowsy or confused that they refuse to take sufficient fluids. Furthermore, the solution may be irritating to the gastric mucosa. There is evidence that the absorption of salt solution from the intestinal tract may be retarded and impaired. This was observed by Hartman and Major who used dogs in their experiments.<sup>10</sup> Vomiting and insufficient fluid intake during treatment may result.

*Intravenous physiologic salt solution during pyrotherapy:* With the concentration used (0.9%), it would be necessary to give 3000 to 4000 cc. of the solution in order to administer sufficient salt to make up the loss from the body. At times this may be technically impossible in uncoöperative patients. Intravenous infusion of such a large amount of fluid would require 3 to 4 hours of time. The possibility of overburdening the heart and of resultant pulmonary edema should be considered.

*Subcutaneous physiologic salt solution:* This method is painful and slow. We have observed large areas of painful induration and persistent edema at the site of injection resulting from this procedure.

**Intravenous Hypertonic Salt Solution.** It was believed that the drawbacks to the methods of administration mentioned above might be largely overcome by the use of intravenous hypertonic sodium chloride solution. Five hundred centimeters of 5% salt solution were administered immediately preceding the induction of artificial fever, and an attempt was made to evaluate this procedure. This dose of salt was decided upon as the average loss of sodium chloride during pyrotherapy is approximately 25 gm.<sup>6,13,26</sup>

Such concentrations of salt have been known to cause diuresis,<sup>20</sup> which would be obviously undesirable because of resultant dehydration. However, according to Baldes,<sup>1</sup> the beginning of diuresis from such solutions is somewhat delayed. We assumed that this delay would be long enough to prevent diuresis because the rise in body temperature would cause a shift of water excretion from the kidneys to the sweat glands. This was apparently confirmed by the fact that we did not observe any diuretic effect in our patients.

It has been stated that excessive doses of salt may cause disturbances in heat regulation, with dangerous secondary effects. However, with the relatively small dosage used in our patients, no effect of this kind was observed.

It has been shown that such amounts of salt solution, if properly prepared without bacterial contamination, do not cause rises in temperature.<sup>5,9,22</sup> Administration at the rate of 500 cc. of 5% solution per hour is considered safe.

**Methods of Investigation.** In a preliminary study it was found that nausea and vomiting occurred in approximately the same percentage of patients (about 60%) when plain water was given as when saline solution was administered orally. It was therefore decided to compare the effects of plain water given by mouth to the results obtained when an intravenous infusion of 500 cc. of 5% saline solution as well as water was given immediately preceding pyrotherapy.

Patients suffering from general paresis, taboparesis, tabes dorsalis, meningovascular syphilis and various complications of gonorrhea were treated by artificial fever therapy with the blanket method.<sup>8</sup>

The axillary temperature of patients with syphilis is raised to 39.5° C. (103.1° F.) during the first treatment, to 40° C. (104° F.) during the second, and to 40.5° C. (104.8° F.) during the third and all consecutive treatments. The temperature of patients with gonorrheal complications is raised to 39.5° C. during the first treatment, to 40.5° C. during the second, and 41° C. (105.8° F.) during all following treatments.

The temperature of patients with syphilis or gonorrhea is maintained at the maximum desired height for 5 hours. Treatment is given with the patient in a fasting state or following a light breakfast consisting only of coffee and two slices of toast. Two hours after treatment, the patient is allowed to eat a light dinner. Fruit juices are usually withheld for 24 hours since they have a tendency to cause vomiting.

A full course of pyrotherapy consists of 10 treatments for patients with syphilis and 8 of those with gonorrhea. However, several of our patients for personal reasons or because of intolerance to the treatments were unable to receive the full course. The patients were all ambulatory and were hospitalized for only 24 hours for each treatment.

Intake, including intravenous infusion, and urine output and vomitus, were measured and the amounts were tabulated for each treatment. The frequency and duration of nausea and the incidence of vomiting were recorded. Between treatments the patients were questioned as to their subjective reactions such as discomfort from heat, feeling of weakness, debility, and so on. All reactions occurring during treatment, and especially those necessitating termination of treatment before the end of the 5-hour period, were recorded. Each patient was weighed without clothes immediately preceding treatment, and again 24 hours later just before discharge from the hospital.

The blood pressure was measured before and after treatment and before discharge by the usual auscultatory method with the mercury sphygmomanometer.

Of the 23 patients studied, 3 were excluded from the comparative series because their nausea and vomiting was caused by morphine sulphate given routinely for sedation. This left a total of 20 patients for comparative study.

A total number of 150 pyrotherapy treatments were given. The patients received 500 cc. of 5% intravenous saline solution at room temperature for each of the first 4 or 5 treatments. They were allowed to drink plain tap-water at room temperature as desired, except that the fluid intake was not permitted to exceed 1000 cc. per hour. In the remaining treatments of the course, usually about 3 or 4, depending on the total number, the administration of saline solution was omitted. During these treatments also the patients were allowed to drink tap-water as before, again not to exceed an intake of 1000 cc. per hour.

**Results.** Of the total 150 fever treatments, 60 treatments were accompanied only by tap-water given by mouth. Ninety treatments were accompanied by the preliminary administration of 500 cc. of 5% saline intravenously and tap-water by mouth.

This difference in number of treatments is explained by the fact that the patient was sometimes unable to take a full course of treatments.

The results were as follows:

(a) *Nausea and Vomiting.* Of a total of 60 treatments without the giving of saline solution, 36 (60%) were accompanied by nausea and vomiting. Vomiting occurred 114 times during these 36 treatments, or an average of 3.16 times per treatment.

Of a total of 90 treatments, preceded by intravenous saline solution, 22 (24.5%) were accompanied by nausea and vomiting. Vomiting occurred 56 times during these 22 treatments, or an average of 2.55 times per treatment.

In order to study the degree of severity of nausea, description of this reaction was specified as:

Mild nausea: duration not exceeding 15 minutes.

Moderate nausea: duration not exceeding 2 hours.

Severe nausea: longer duration (usually 24 hours or longer).

This last type of nausea was exhausting, and prevented the patient from taking anything by mouth.

TABLE 1.—NAUSEA AFTER ADMINISTRATION OF WATER AND INTRAVENOUS SALINE.

	Water given by mouth.	Saline given intravenously.
Slight nausea:		
No. of treatments . . . . .	24	19
Per cent . . . . .	65	85
Moderate nausea:		
No. of treatments . . . . .	2	2
Per cent . . . . .	7	10
Severe nausea:		
No. of treatments . . . . .	10	1
Per cent . . . . .	28	5
Total treatments . . . . .	36	22

This shows that severe nausea occurred almost 6 times as frequently when the administration of saline solution was omitted. In several cases the administration of saline solution entirely prevented nausea and vomiting. In no case did it increase these symptoms.

The objection might be raised that nausea and vomiting occurred less frequently in the saline experiment because the saline solution was given during the first two treatments when the temperature was lower than maximal. However, it was found that nausea and vomiting occurred twice as frequently during the first two treatments as in the following three treatments in which maximal temperatures were attained. This conformed with previous ob-

servations, showing that the incidence of nausea and vomiting in general was highest for the first two treatments and did not increase, but rather decreased, toward the end of the course of pyrotherapy.

(b) *Intake and Output.* When saline solution was administered, the total average fluid intake was 3700 cc. per 24 hours, and the total average fluid output was 620 cc. per 24 hours. Fluid intake fluctuated between a maximum of 5700 cc. and a minimum of 1650 cc. Fluid output fluctuated between a maximum of 2700 cc. and a minimum of 400 cc. except in 1 case in which there was no urinary output at all for 24 hours.

When water alone was given, the total average fluid intake was 2700 cc. per 24 hours and the total average fluid output 880 cc. per 24 hours. Fluid intake fluctuated between a maximum of 5300 cc. and a minimum of 600 cc. per 24 hours. Fluid output fluctuated between a maximum of 2200 and a minimum of 150 cc. except in the case of 1 patient who had no urinary output for 24 hours.

(c) *Influence on Weight.* *With Salt:* Following 25 of the 90 saline treatments there was a gain in weight. The average gain was 700 gm. The maximum gain for a single individual was 1900 gm. Following 2 treatments there was no change in weight. Following 63 treatments there was a loss in weight, the average loss being of 1000 gm. The maximum loss for a single individual was 3600 gm.

*Without Salt:* Following 60 treatments when water only was given, there was only one gain in weight (300 gm.); following 3 treatments there was no change; following 56 treatments there was loss in weight with an average loss of 3000 gm. The maximum loss for a single individual was 5200 gm.

(d) Saline solution improved subjective tolerance to heat in many instances. Many patients were less restless following its administration, and there was a definite decrease in the incidence of post-therapeutic weakness and debility. Inability to tolerate treatment for the full 5-hour period and discontinuance of treatment because of anxiety states, delirium and dangerous increase in pulse rate occurred more frequently when saline solution was omitted.

(e) There was no significant effect of saline solution intravenously on the blood pressure. In general, there was a tendency for the blood pressure to fall after artificial fever treatments.

*Untoward Reactions.* Four venous thromboses occurred following intravenous 5% salt solution that were localized to the site of injection. In 2 cases this was due to faulty intravenous technique with leakage of saline solution into the subcutaneous tissue. No other untoward effects were observed in this series of 20 patients. However, after completing this series we have used saline solution in about 30 additional patients and on 2 occasions have observed slight chills following its administration. These chills were accom-

panied by slight rises in temperature which shortened the time required to raise the patient's temperature to the desired maximal point. We are unable to say definitely whether these chills were caused by faulty preparation of the solution used or whether they were caused by the salt itself.

*Contraindications.* We did not observe any undue fluctuation in blood pressure following the administration of hypertonic saline solution. Nevertheless, we do not advise its use in patients with advanced cardio-reno-vascular disease and marked hypertension, and so on.

*Summary and Conclusions.* 1. The intravenous use of hypertonic saline solution (5%) immediately preceding artificial fever therapy is advocated.

2. This procedure was found to be of considerable value in reducing the incidence, frequency and severity of nausea and vomiting. It was also effective in reducing the incidence and severity of reactions of intolerance to heat and post-therapeutic debility.

3. The administration of salt by this method is simple and rapid. It is accompanied by very few untoward reactions and little or no discomfort.

4. The intravenous administration of hypertonic saline solution preceding pyrotherapy has a marked tendency to increase fluid intake and to diminish fluid output. As evidenced by changes in weight, there is a tendency toward retention of fluid. This retention seems to alleviate or prevent certain undesirable reactions that are seen in artificial fever therapy. The therapeutic effect is probably explained chiefly by the osmotic action of the sodium chloride.

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REGULATION OF CIRCULATION IN THE SKIN AND MUSCLES  
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THE investigations that we have carried on during the past 3 years<sup>1,2</sup> have shown that the regulation of the circulation in the skin differs from that in the muscles of the lower extremities. In a previous publication, we stated that lumbar sympathetic paralysis increases the circulation to the skin of the lower extremities, but does not increase the circulation to the calf muscles. Subsequently, Grant<sup>3</sup> came to a similar conclusion in regard to the muscles of the upper extremities utilizing the plethysmographic method. In this paper, more detailed data are presented and new experiments on the effects of typhoid vaccine are reported. We have continued to use direct temperature measurements, as this method appears to us to be the best available for the separate and simultaneous study of circulatory changes occurring in the skin and muscles of the extremities of the living human subject.

Seven methods of influencing the circulation were employed in this study. They consisted of: *a*, Lumbar paravertebral injections of alcohol; *b*, spinal anesthesia; *c*, intravenous injections of hypertonic sodium chloride solution; *d*, intravenous injections of physiologic sodium chloride solution; *e*, intravenous injections of adrenalin; *f*, immersion of forearms in hot water; *g*, intravenous injections of typhoid vaccine.

**Procedure.** Thermocouple needles, insulated along the shaft so that only the tips recorded temperature, were inserted into the calf muscles. The skin over the muscle area studied was first cocaineized so as to avoid pain and apprehension due to insertion of the needles. Stabilization of temperature was obtained before any procedures were begun. Simultaneous observations of the skin surface temperatures of the great toes were taken with a skin surface thermocouple, and the rectal temperature was noted by means of a recording resistance rectal thermometer. All temperatures were observed at 10-minute intervals for a period of 2½ to 5 hours after stabilization.

Subjects were selected for these studies from among the men coming for examination or treatment in the clinic for peripheral vascular disease.

\* Aided by a grant from the Council on Physical Therapy of the American Medical Association.

Some of them had thrombo-angiitis obliterans, others arteriosclerotic peripheral vascular disease. A few patients showed impaired circulation in one extremity, but no evidence of arterial involvement in the other leg. Since studies were made simultaneously in both lower extremities, such patients offered an opportunity to observe changes where the circulation was normal and where it was deficient.

GROUP A. Ten patients were treated by paravertebral injections of alcohol in the lumbar region. The technique used was that described by Labat.<sup>6</sup> Two needles, 12 cm. long, were inserted about 1 inch apart. From a point 7 cm. from the midline the needles were directed obliquely so that they just passed the vertebral column. Novocaine (10 cc.) was then deposited through each needle along the course of the lumbar sympathetic trunk. If satisfactory elevation of temperature in the foot resulted, 10 cc. of alcohol was injected without changing the position of the needles.

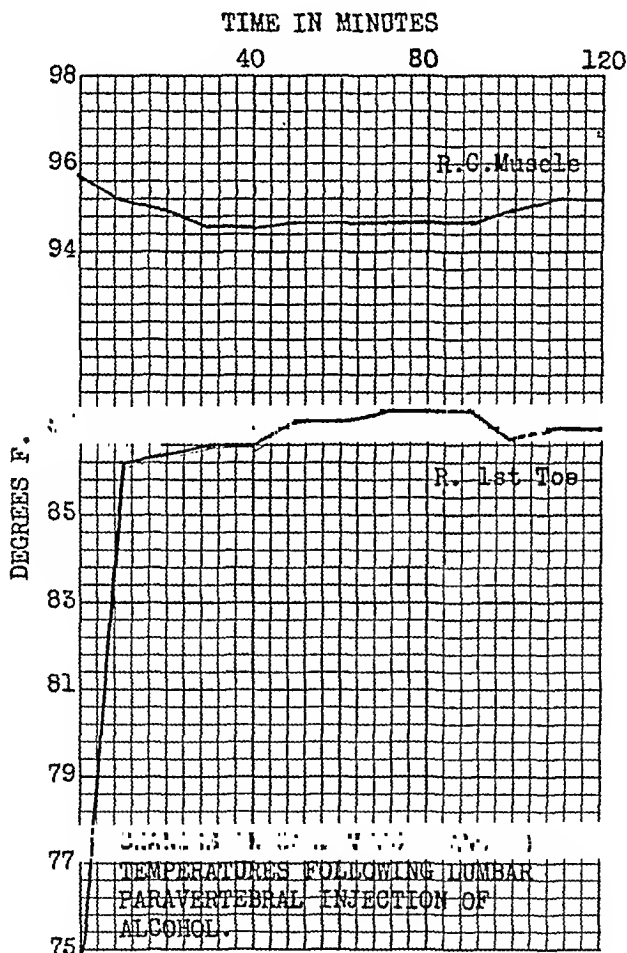


CHART I.

The initial temperature of the toes varied with the room temperature, being lower in a cold room and higher in a warm room. The elevation in skin temperature following paravertebral injections varied from 2° to 10° F., depending upon the initial temperature of the toes. In most cases the muscle temperature dropped from 1° to 2° F. In 3 cases a rise of

0.5° F. took place in the muscles. Table 1 summarizes the data obtained by this procedure. A typical temperature chart is shown in Chart 1).

TABLE 1.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING LUMBAR PARAVERTEBRAL INJECTION OF ALCOHOL.

Name.	Date.	Side injected.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
			Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
H. B.	12/ 4/35	Right	98.8	98.8	..	..	95.0	94.2	..	..	71.8	85.3
M. F.	5/ 8/37	Right	99.0	99.0	94.0	93.0	95.5	96.0	81.5	78.8	81.5	85.1
R. G.	4/ 3/37	Right	98.4	98.4	96.2	96.6	95.8	96.3	86.0	89.0	86.0	84.4
I. J.	12/ 2/35	Right	..	..	..	..	95.5	91.5	..	..	82.6	91.0
H. L.	12/ 2/36	Left	99.4	99.4	97.9	98.4	96.0	95.0	77.0	86.0	74.0	77.0
J. S.	12/11/36	Left	98.4	98.6	96.7	95.5	97.4	99.0	77.0	80.0	79.0	86.0
A. F.	11/20/37	Left	97.7	97.3	92.4	91.2	95.4	86.0	68.0	71.0	68.0	66.0
H. L.	6/ 7/37	Left	99.4	98.6	94.7	94.0	95.4	98.0	80.0	80.0	82.0	79.0
H. L.	7/15/37	Left	99.2	99.2	97.0	95.3	95.4	94.5	84.0	86.0	79.0	81.0
C. N.	5/ 1/37	Right	99.3	99.3	94.4	90.0	95.2	97.2	82.0	79.0	78.0	84.0
Av.	...	...	98.8	98.8	95.5	94.7	95.7	94.7	78.8	81.0	78.2	81.9

*Comment.* In these 10 cases, sympathetic paralysis produced by paravertebral injection of alcohol was followed by a sharp increase in the skin surface temperature and no corresponding elevation in the muscle temperature. Since all sympathetic fibers to the lower extremities might not be paralyzed by this type of injection, the experiments were repeated using spinal anesthesia.

GROUP B. The usual technique for spinal anesthesia was employed. A lumbar puncture was done at the level of the fourth lumbar vertebra, 120 mg. of novocaine crystals were dissolved in about 3 cc. of spinal fluid and reinjected. With this procedure *all* nerve fibers to the lower extremities were paralyzed. The elevation of skin surface temperature varied from 5° to 15° F. The muscle temperature dropped from 1° to 1.5° F. and the rectal temperature dropped 0.5° to 2° F. Table 2 summarizes the data; Chart 2 shows a typical temperature chart.

*Comment.* In this group of cases with complete nerve paralysis following spinal anesthesia, the skin surface temperature rose markedly. The calf muscle temperature dropped approximately 1° F. The tests with spinal anesthesia thus confirm those with paravertebral injections of novocaine and alcohol, and demonstrate that paralysis of the sympathetic fibers is not followed by any increase of circulation in the calf muscles.

GROUP C. Since injections of hypertonic sodium chloride solution have been employed for many years in the treatment of patients with peripheral vascular disease, the effects of such injections upon the skin and muscle temperature were studied. Following the intravenous injection of 300 cc. of 5% sodium chloride solution, given rapidly, there was a marked increase in skin surface and calf muscle temperature. The rectal temperature rarely changed. This group was the only one studied which showed an increase in *both* the skin surface and the calf muscle temperatures. Table 3 summarizes the data; Chart 3 is a typical temperature curve.



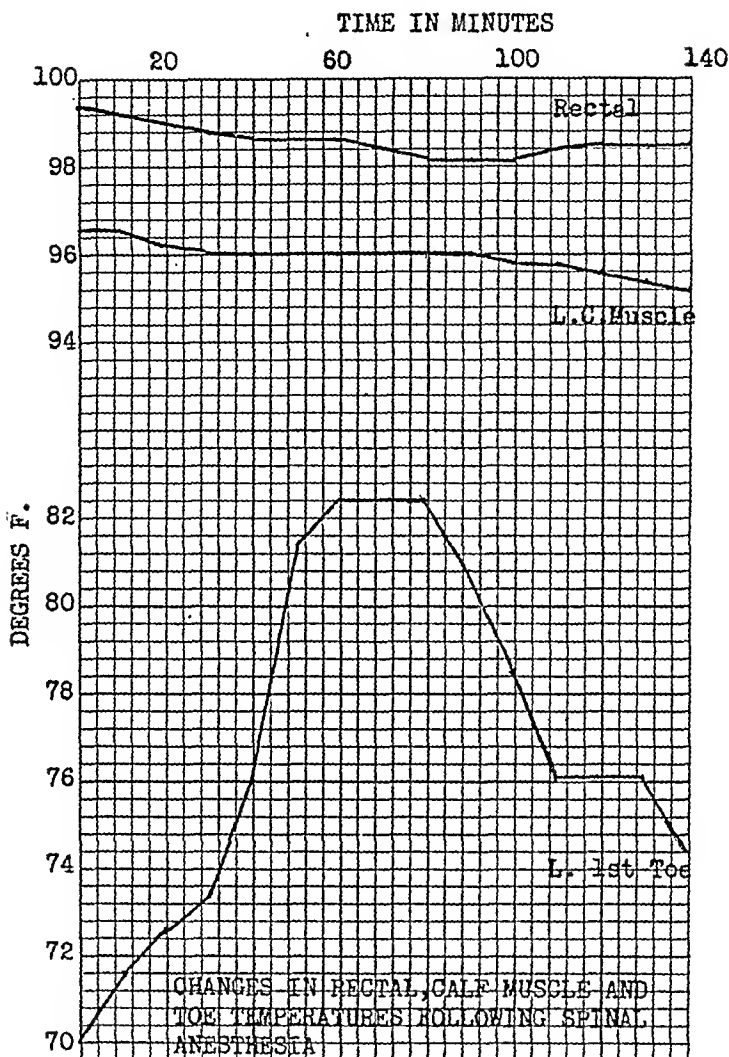


CHART 2.

TABLE 2.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING SPINAL ANESTHESIA.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
H. B. . .	12/11/35	99.5	98.4	..	..	95.0	93.7	78.0	87.8	75.0	89.0
T. K. . .	11/27/37	99.5	98.4	96.5	94.5	96.2	96.0	69.8	82.4	71.0	80.0
E. P. . .	12/18/37	99.4	97.4	97.2	95.0	97.7	94.8	82.0	87.0	71.0	87.0
A. S. . .	12/15/37	99.4	97.3	95.7	94.0	98.2	95.4	64.0	77.0	68.0	83.0
R. G. . .	12/ 4/37	98.5	98.3	97.7	96.5	97.7	96.5	89.0	92.0	87.0	89.0
Average. .	...	99.2	98.0	96.8	95.0	96.9	95.3	72.5	85.2	74.4	85.6

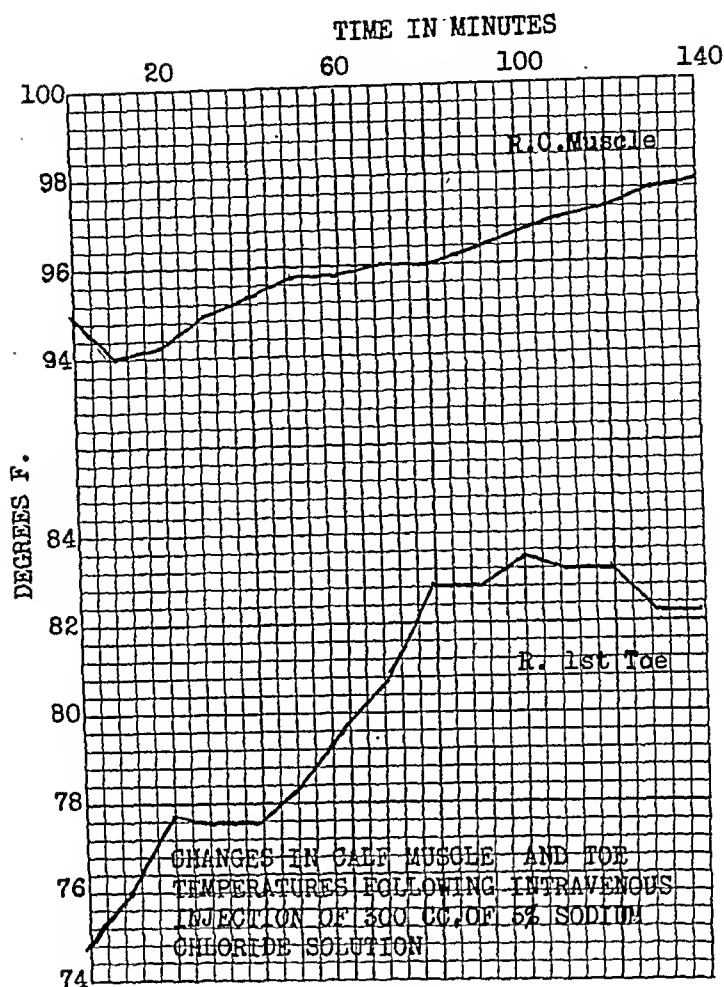


CHART 3.

TABLE 3.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING INTRAVENOUS INJECTION OF 300 CC. OF 5% SODIUM CHLORIDE SOLUTION.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
H. B. . .	5/ 5/37	98.0	98.0	96.0	97.7	94.2	94.8	88.5	88.5	82.2	84.2
R. G. . .	9/30/37	99.2	99.2	96.0	99.0	96.0	97.0	77.0	82.2	75.0	85.0
R. G. . .	10/ 7/37	99.5	99.5	96.5	98.7	95.5	97.2	84.2	88.0	82.4	88.2
I. J. . .	12/ 2/35	99.0	99.0	91.5	93.3	90.0	90.7	86.0	87.0	84.0	86.9
R. L. . .	9/28/36	99.4	99.4	97.3	99.0	95.0	97.7	73.7	81.3	74.8	82.2
T. S. . .	3/ 9/37	99.0	99.0	95.6	96.7	95.4	96.2	75.0	79.0	76.0	81.0
A. S. . .	10/29/37	98.8	99.0	95.0	96.3	96.0	97.8	75.0	80.0	68.0	69.0
S. S. . .	5/ 7/37	98.9	98.9	96.3	96.8	97.3	98.8	80.0	85.6	80.3	87.0
C. N. . .	2/23/37	99.4	99.4	96.0	97.0	96.5	97.5	77.0	84.0	74.0	82.0
J. S. . .	11/20/36	96.4	96.4	96.7	97.4	95.2	96.0	85.0	86.0	84.0	86.0
Average .	...	98.8	98.8	95.7	97.2	95.1	96.4	80.1	84.2	78.1	83.1

GROUP D. For purposes of control and to determine if the injection of 300 cc. of fluid might not in itself produce the changes noted in Group C, 10 patients were given intravenous injections of 300 cc. of physiologic saline. There were no changes in skin surface, calf muscle or rectal temperatures. Table 4 is a summary of the findings. Chart 4 is a typical temperature curve.

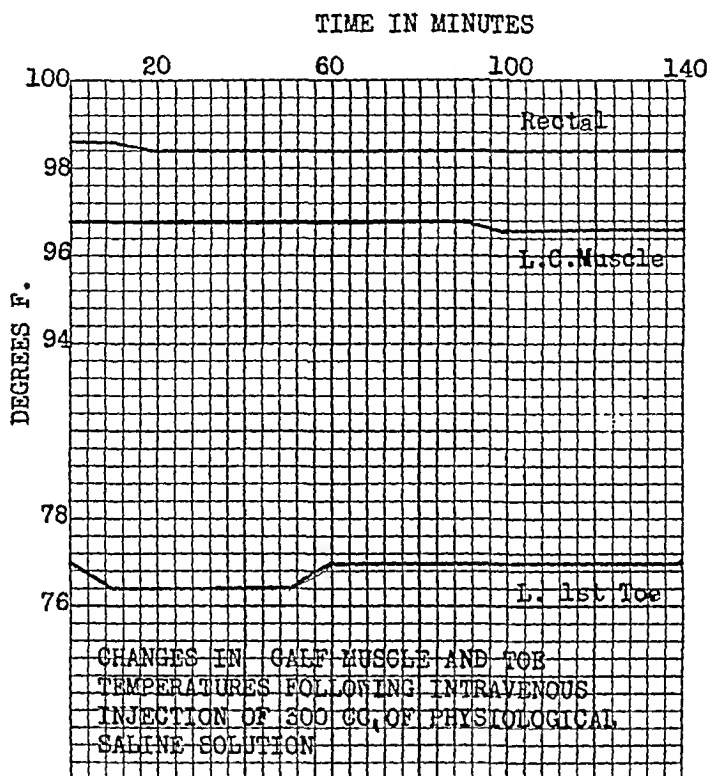


CHART 4.

TABLE 4.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING INTRAVENOUS INJECTION OF 300 CC. OF PHYSIOLOGIC SALINE SOLUTION.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
A. F. . .	2/11/37	99.4	99.4	95.8	95.6	94.5	94.5	79.5	80.9	75.0	76.0
R. G. . .	2/20/36	98.5	98.5	96.4	97.1	96.6	96.9	84.0	85.0	83.0	84.0
T. K. . .	11/ 1/37	99.8	99.7	96.8	96.7	97.8	98.0	77.0	76.5	77.5	78.8
H. L. . .	5/26/37	98.8	98.8	95.1	95.0	93.2	92.8	83.8	84.3	88.3	88.5
C. N. . .	3/ 2/37	98.8	98.8	94.5	94.5	95.5	95.5	79.0	80.0	80.0	80.4
S. R. . .	11/27/36	99.4	99.4	96.6	96.8	97.1	97.5	75.0	76.0	81.0	83.0
T. S. . .	2/27/37	99.0	99.0	96.0	95.7	93.9	94.0	77.8	77.4	76.6	76.8
A. S. . .	10/25/37	98.8	98.8	95.2	94.8	96.0	95.6	68.0	68.0	68.0	68.0
S. S. . .	5/17/37	98.8	98.8	95.9	96.3	97.3	97.1	85.0	85.2	84.7	84.2
W. W. . .	7/20/36	99.4	99.4	92.2	92.2	..	..	80.0	83.0	83.0	84.0
Average .	...	99.0	99.0	95.4	95.5	95.7	95.7	78.9	79.6	79.7	80.3

GROUP E. Since paralysis of the sympathetic nerve fibers resulted in an increase of skin surface temperature without a corresponding rise in muscle, we studied the effects of sympathetic stimulation. For this purpose 1 or 2 cc. of adrenalin chloride (1 to 1000) was diluted in 300 cc. of physiologic saline and given intravenously by the slow drop method. We found that while the skin surface temperature dropped approximately  $6^{\circ}$  F., the calf muscle temperature rose about  $2^{\circ}$  F. and the rectal temperature rose  $0.3^{\circ}$  F. Table 5 summarizes the findings in this group; Chart 5 is a typical temperature curve.

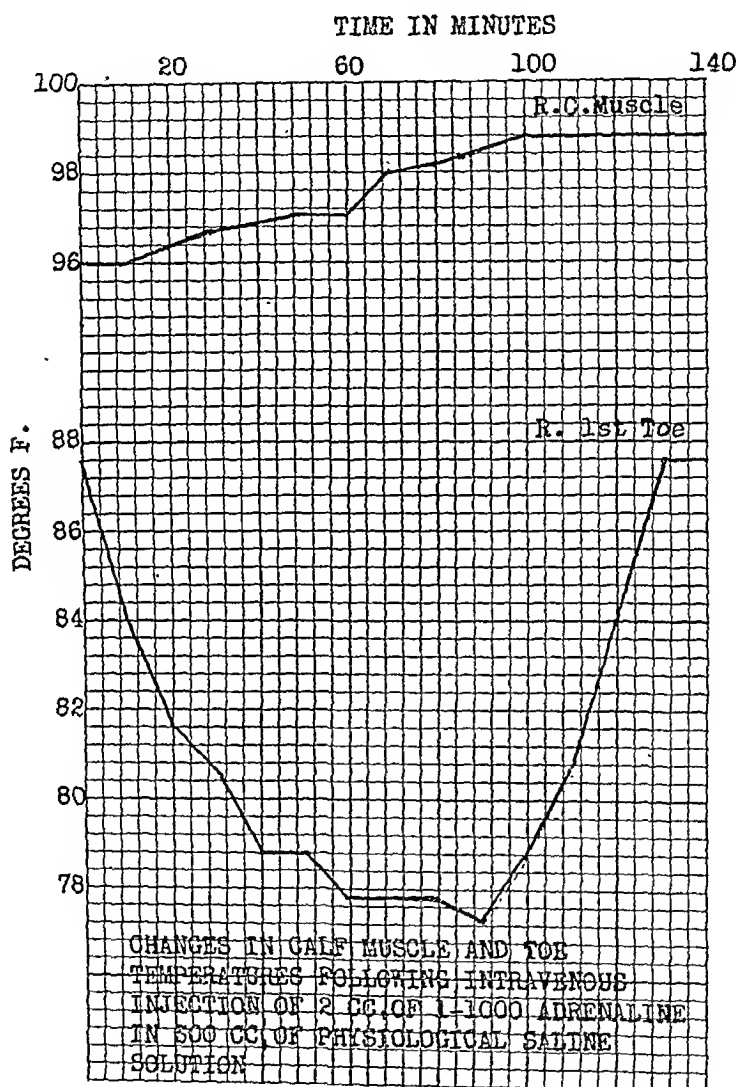


CHART 5

*Comment.* The rise in calf muscle temperature indicates an increased circulation in these tissues. Plethysmographic studies by Hoskins, Gunning and Berry<sup>5</sup> have likewise shown that the circulation in the muscles is increased by injections of adrenalin. However, such an increase also occurs in muscles deprived of sympathetic innervation. Grant<sup>4</sup> has shown such changes after adrenalin injection.

tions in the forearm muscles of individuals subjected to sympathetic ganglionectomy. The increased circulation in the muscles therefore cannot be attributed to sympathetic stimulation, but is due to some hormonal or chemical effect. It is important to note that opposite changes occur in skin and muscle at the same time, *i. e.*, a decrease of circulation in the skin and an increase in the muscle.

TABLE 5.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING INTRAVENOUS INJECTION OF 2 CC. OF 1 TO 1000 ADRENALIN IN 300 CC. OF PHYSIOLOGIC SALINE SOLUTION.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
H. B. . . .	11/ 3/37	98.3	98.8	96.8	97.4	95.0	98.0	89.6	85.1	80.6	75.2
A. F.. . .	10/ 9/37	98.8	98.8	94.0	96.0	94.7	97.6	76.0	74.0	75.0	72.0
A. F.. . .	11/ 6/37	98.6	99.0	93.5	96.4	94.3	98.0	77.0	75.2	80.6	76.1
R. G. . . .	11/ 9/37	98.6	99.5	96.3	97.5	96.0	98.7	90.0	82.0	87.8	78.8
H. L. . . .	11/ 3/37	99.3	99.5	95.8	97.0	93.3	94.7	77.0	75.0	77.0	74.0
J. S. . . .	11/12/37	97.0	97.0	96.0	96.4	94.8	96.0	87.8	79.7	84.2	77.0
V. T. . . .	11/11/37	97.8	98.5	97.0	97.4	97.2	98.2	87.8	76.0	86.9	72.0
H. L. . . .	11/ 2/37	97.4	97.5	94.8	95.7	96.8	97.8	87.8	85.0	87.8	85.0
Average . . .	...	98.2	98.5	95.5	96.7	95.2	97.4	84.0	79.0	82.5	76.3

GROUP F. The relationship between skin surface and calf muscle temperatures was further studied when the forearm was placed in hot water. For this purpose a water bath at 114° F. was used, and the forearm was kept immersed for 45 minutes or longer. A marked rise occurred in the skin surface temperature of the toes but was not accompanied by a similar change in the calf muscle temperature. The rectal temperature rose approximately 0.5° F. Table 6 summarizes the data; Chart 6 presents a typical temperature curve.

*Comment.* The mechanism by which hot arm baths affect the surface temperature of the toes has been studied by Pickering.<sup>7</sup> He showed that the warmed blood returning from the upper extremities affected the heat regulating center in the brain, and that secondary nervous impulses to the lower extremities resulted in vasodilatation. Such nervous impulses are carried by the sympathetic nervous system. We have shown that the changes noted in the skin surface temperature of the toes following hot forearm baths were not accompanied by corresponding changes in the calf muscles.

GROUP G. Fever was produced by the intravenous injection of typhoid vaccine in this group of patients. Initial injections contained 5,000,000 typhoid bacilli. This amount was progressively increased until the systemic temperature was raised 2 or 3° F. In the majority the rise in systemic temperature occurred about an hour after the injection. The rise in body temperature was accompanied by a gradual fall in calf muscle temperature. These changes continued throughout the period studied and were unaltered by the occurrence of chills and tremors. The skin surface temperature rose

before the onset of the chill but dropped when the chills occurred. It always rose above the initial level after the chills subsided. The data are summarized in Table 7; Charts 7 and 8 give typical temperature curves.

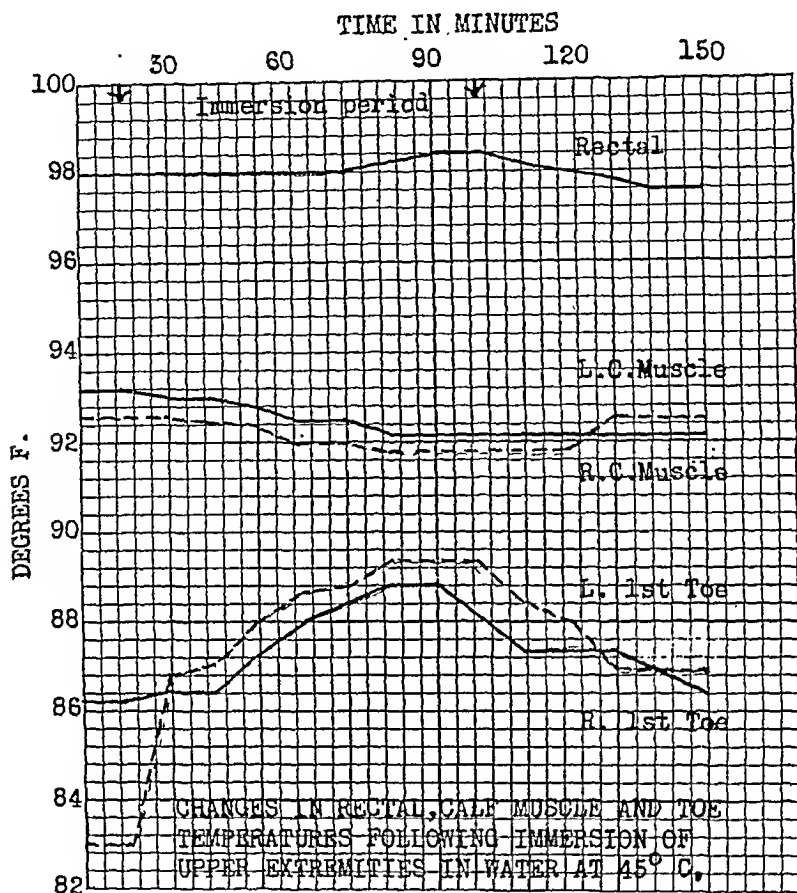


CHART 6.

TABLE 6.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING IMMERSION OF UPPER EXTREMITIES IN WATER AT 45° C.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
H. Z. . .	11/19/35	..	..	93.0	90.7	..	..	80.0	86.0	..	..
M. S. . .	6/27/38	97.6	99.2	90.3	88.8	90.3	90.0	76.8	89.1	76.8	89.0
A. S. . .	11/10/38	98.2	98.2	91.7	93.7	95.6	95.0	72.0	91.0	76.0	90.0
E. D. . .	10/31/38	98.2	99.5	95.2	91.2	94.5	91.4	73.9	85.0	79.3	83.0
L. . .	11/ 2/38	97.7	98.2	92.5	91.0	92.5	92.5	74.6	77.8	74.6	76.0
A. S. . .	11/ 3/38	99.7	99.8	96.7	96.6	97.7	96.6	81.7	88.9	80.8	88.9
W. . .	10/27/38	97.0	97.7	95.0	94.6	94.0	92.6	83.0	84.0	80.0	84.0
A. P. . .	10/20/38	97.6	98.2	96.2	95.5	95.6	95.6	82.4	83.0	84.0	85.6
J. B. . .	10/19/38	98.0	98.3	92.5	92.0	93.2	92.2	86.9	88.0	86.2	87.4
S. R. . .	10/17/38	96.7	97.0	96.3	95.0	96.7	96.6	77.8	89.0	80.0	87.4
Average . .	...	97.8	98.4	94.2	92.9	94.4	92.5	78.9	86.2	79.7	85.7

TABLE 7.—CHANGES IN RECTAL, CALF MUSCLE AND TOE TEMPERATURES FOLLOWING INTRAVENOUS INJECTION OF TYPHOID VACCINE.

Name.	Date.	Rectal.		Left calf muscle.		Right calf muscle.		Left toe.		Right toe.	
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
M. K. . .	5/13/38	99.3	104.7	94.5	92.0	92.3	90.6				
A. Z. . .	11/29/38	98.4	101.0	97.0	93.8	96.4	93.4	70.6	73.0	70.6	73.3
A. P. . .	3/ 4/38	99.2	100.7	96.0	93.7	96.4	95.6	87.6	85.0	86.0	87.2
H. G. . .	2/ 5/38	98.4	100.6	94.6	92.0	94.0	91.6	70.5	73.0	72.2	73.4
R. N. . .	3/21/38	99.2	101.2	97.0	95.6	95.4	93.6	81.1	87.4	82.6	87.8
J. F. . .	3/28/38	99.2	100.0	96.0	94.0	96.0	94.2	75.2	85.0	73.1	75.8
D. L. . .	5/10/38	96.7	98.7	94.7	91.6	94.2	91.0	73.4	74.5	72.5	73.9
L. A. . .	2/ 9/38	97.8	100.6	94.8	91.4	93.8	91.2	68.6	77.2	70.2	75.2
V. T. . .	3/30/38	98.2	100.7	96.8	95.5	96.0	95.4	81.3	90.2	83.1	86.7
W. R. . .	5/16/38	99.4	103.7	95.7	94.0	95.7	94.0	95.4	98.2		
Average .	...	98.6	101.7	95.7	93.4	95.0	93.0	70.4	82.7	76.4	78.2

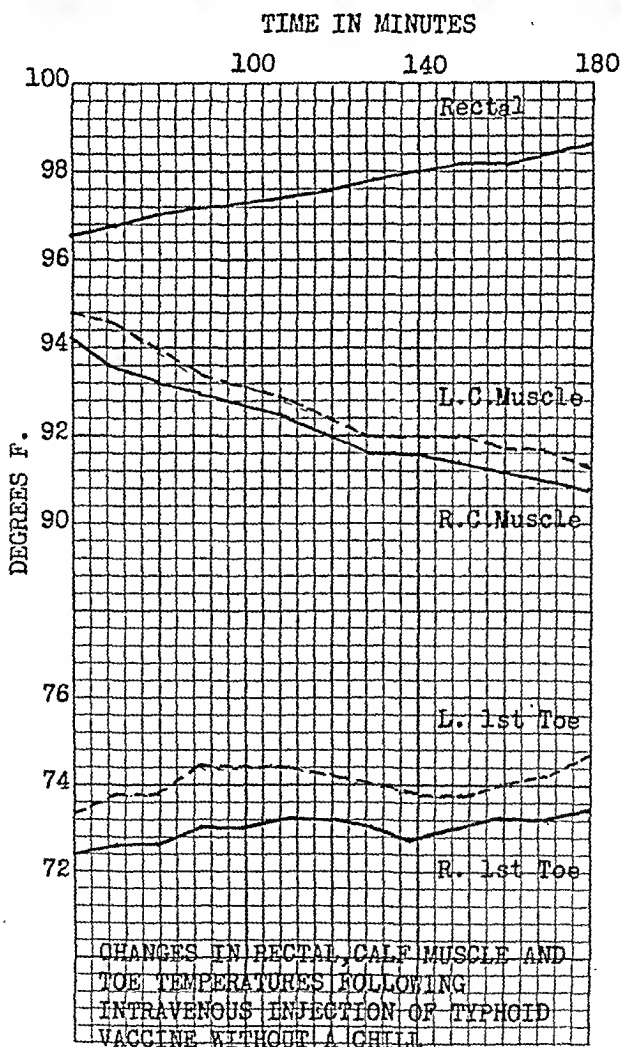


CHART 7.

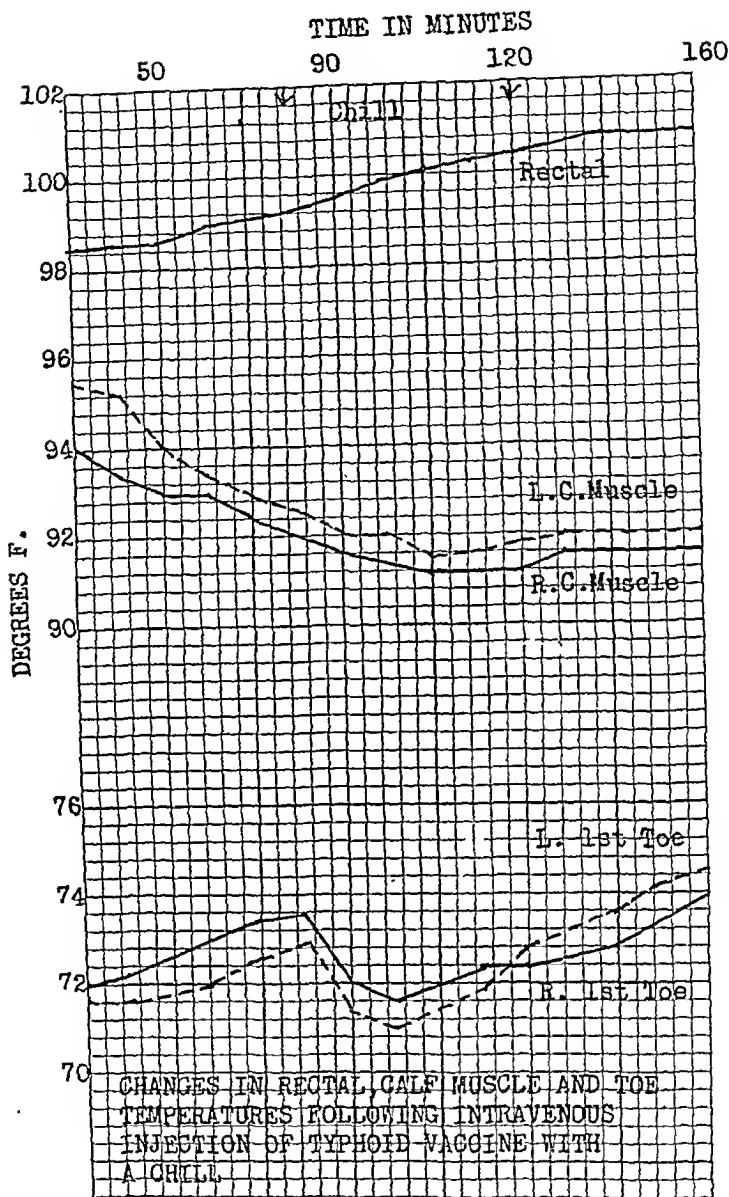


CHART 8.

**Discussion.** Seven different methods were employed to alter the circulation in the lower extremities. In all but one of them, changes in the circulation occurred in the skin with opposite or no changes in the muscles. These observations indicate that the circulatory response to therapeutic procedures is not necessarily parallel in the superficial and deep structures. Since sympathetic paralysis fails to increase the circulation of the muscles, the use of ganglionectomy for the treatment of intermittent claudication has no physiologic basis. Of all the methods studied, the use of intravenous injections of hypertonic salt solution is unique in its ability to increase the circulation in both the skin and muscles.



The major problem in the treatment of patients with peripheral vascular disease is the relief of intermittent claudication. Practically all patients with circulatory deficiency present this symptom and in more than one-half of them this is the only serious complaint. To relieve it, therapeutic procedures must be used that will increase the circulation in the muscles. On the other hand, when ulceration is present, a method of treatment which will increase the circulation of the skin is desirable.

It is no longer justifiable to conclude that an evident increase in the circulation in the skin is accompanied by a similar increase in underlying muscles. In the future each method of treatment must be studied to determine to what extent it independently affects the circulation of the muscles and the skin. It will then be possible for the clinician to utilize that method which answers his specific needs.

**Conclusion.** The circulation in the skin and muscles of the extremities is independently regulated.

The blood flow in the muscles of the extremities is not directly controlled by the sympathetic nervous system.

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### RAT MORTALITY FOLLOWING SODIUM TUNGSTATE INJECTION.

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THE most extensive study of this subject was reported by Bernstein-Kohan.<sup>1</sup> From 12 rats used (body weights varying between 75 and 225 gm. with no mention made of age, sex, or diet), Bernstein-Kohan concluded that subcutaneous injection of 540 mg. of sodium tungstate (equivalent to 338 mg. of W metal) per kg. body weight was the smallest dose producing death.

In connection with another problem, it was necessary to examine critically the findings of Bernstein-Kohan. This led to a study of certain factors influencing the effects of subcutaneously injected sodium tungstate.

**Experimental.** The animals were chosen from the College colony of mixed Wistar albino and Minnesota piebald rats. Mixed litters were used with approximately equal numbers of each sex. The diet in each case was Purina dog chow.

In order to obtain the body weight without the varying weight of intestinal ballast, the rats were in each case starved about 24 hours before the injection. The sodium tungstate solution was of such concentration that 0.5 cc. was used for each 100 gm. body weight.

**Postprandial Effect.** The influence of the digestive and metabolic processes upon the toxicity of the sodium tungstate was determined by dividing 54 rats of the same age into 2 groups of equal size. The animals were starved about 24 hours. The first group was weighed and each rat given its calculated dose, and then fed. The second group was weighed, and then fed. One to three hours later each animal was given the dose calculated from the body weight before eating. In the first group injected, there was a mortality of 40.7%; in the latter group injected during active metabolism there was a mortality of 14.8%.

**Age Effect.** Rats of the same age were grouped and starved about 24 hours. Each rat was weighed, injected with sodium tungstate (W equivalent of 150 mg. per kg. body weight), then fed. The mortality of each group is shown in Table 1.

TABLE 1.—EFFECT OF AGE UPON MORTALITY.

Age in days	30	44	66	170	195	365	66	180
Mg. W per kg. body wt.	150	150	150	150	150	150	120	120
No. of ani- mals	21	20	39	16	19	29	24	16
% mortality	0.0	30.0	59.0	100.0	89.5	100.0	8.3	87.5

Several additional groups are listed in which a dosage of 120 mg. per kg. was used.

**Sex.** Upon checking through groups in which the mortality was 10 to 80%, the male deaths were slightly more numerous than those of the females, in the ratio of 15:13.

**Mortality Under Controlled Conditions.** Based on the foregoing observations, rats of 66 days were starved about 24 hours, weighed, injected, and then fed. The animals were observed for only 5 days following the injection. The results are found in Table 2.

**Discussion.** For rats, the minimum lethal dose of sodium tungstate, as given by Bernstein-Kohan, is too large. Using Baker's special, chemically-pure, sodium tungstate ( $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ ), the median lethal dose (LD50) appears to lie between 223 to 255 mg. sodium tungstate (140–160 mg. W equivalent) per kg. body weight.

These results were obtained in 66-day-old rats under the special conditions mentioned below.

TABLE 2.—MORTALITY IN THE 66-DAY-OLD RAT.

Mg. W. per kg. body wt.	100	120	140	150	160	170	200	220	250
No. of animals	30	24	33	39	32	27	20	18	4
% mortality	0.0	8.3	6.1	59.0	53.1	63.0	95.0	100.0	100.0

If injected during the period of active metabolism following a meal, the rats succumbed to a lesser extent than when they were injected immediately following a 24-hour starvation period. From this study, it cannot be determined whether the effect is due to diminished absorption or to an altered response to the absorbed tungsten. This is being studied further.

With increasing age there is an increased mortality (Table 1). This cannot be explained solely upon the basis of weight difference, for, within a group of definite age, in many instances, the lightest as well as the heaviest rats died, while those of medium weight survived.

**Summary.** The median lethal dose (LD50) for 66-day-old rats, subcutaneously injected with sodium tungstate after a 24-hour starvation period, appears to lie between 223 to 255 mg. of sodium tungstate (equivalent to 140 to 160 mg. of W).

It is pointed out that there is a definite age effect and that post-prandial conditions markedly influence results.

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## ROTENONE IN THE TREATMENT OF SCABIES.

### A NEW, NONODOROUS, NONIRRITATING FORM OF TREATMENT. PRELIMINARY REPORT.

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THE search for an effective, easily applicable, non-odorous and non-irritating scabeticide is practically as old as the disease itself. A number of remedies have stood the test of time, predominantly sulphur in various forms, pyrethrum, betanaphthol and liquid

styrax. All have, however, certain drawbacks, being either productive of irritation or objectionable because of malodorous, messy or staining properties.

Some time ago Dr. William J. Lentz\* called our attention to the remedy which is the subject of this report, namely, rotenone, which has found wide and successful application in veterinary medicine. It is a common constituent of flea powders, and also used in the form of a 2% acetone-alcohol solution in the treatment of demodectic (follicular) mange. It is likewise widely used as a contact insecticide for agricultural purposes.

Rotenone is a colorless, crystalline, non-nitrogenous substance with a melting point of  $163^{\circ}\text{C}$ . It is practically insoluble in water, but readily soluble in the organic solvents (alcohol, ether, acetone, chloroform, benzene, carbon tetrachloride). Its empiric formula according to Crane<sup>3</sup> is  $\text{C}_{23}\text{H}_{22}\text{O}_6$ . Rotenone was first derived by extraction from derris root (*Derris elliptica*) which is one of a number of tropical marine plants with fish-poisoning properties, and has a rotenone content of from 5 to 9%. It is now more commonly made from the South American cube root (*Lonchocarpus nicou*) which has a rotenone content of approximately 7%. Derris root, administered by mouth, is toxic for most species of animals (Ambrose and Haag<sup>1</sup>), notably guinea pigs and rats, and to a much lesser extent to dogs, producing in large doses death by respiratory paralysis. Rotenone, which is only one of several constituents of derris root, is apparently tolerated in very much larger quantities (Buckingham,<sup>2</sup> Haag<sup>4</sup>), producing a transient gastro-enteritis in sheep, swine and dogs, when given by mouth. When injected subcutaneously or intraperitoneally in the form of a glycol solution, however, it is fatal to guinea pigs and dogs (Haag,<sup>4</sup> and Mathews and Lightbody<sup>5</sup>) and if olive oil or other fats are administered when the drug is given perorally, its toxicity is likewise greatly enhanced, because presence of oil apparently facilitates absorption from the gastro-intestinal tract.

On the other hand, appreciable absorption apparently does not occur from the skin, for Ambrose and Haag<sup>1</sup> were unable to demonstrate absorption of a 10% derris ointment in lanolin in man and rats, and Haag<sup>4</sup> administered a 1% rotenone ointment in petrolatum to rabbits and guinea pigs without evidence of local irritation or absorption. We used a 5 and 10% rotenone ointment in a base of benzoinated lard in the inunction of 2 guinea pigs over a space of 6 months, at the rate of 3 inunctions per week, administering an average of 8.5 gm. rotenone to each pig, without evidence of any toxic effect. When the animals unfortunately succumbed during an epidemic of pneumonia in the animal house, autopsy revealed no pathologic changes except those attributable to pneu-

\* Director of the Small Animal Clinic of the School of Veterinary Medicine of the University of Pennsylvania.

monia. Rotenone was next used on 3 normal human volunteers. A non-oily, emollient, liquid vehicle was purposely selected, namely, a mucilage of quince seed and Irish moss. This has the triple purpose of: 1, serving as a vehicle for rotenone, without favoring its absorption by the presence of oil; 2, acting as an emollient to the irritation and dermatitis so often found in severe scabies; 3, eliminating the objectionable qualities of a greasy, messy form of treatment. The preparation was made up as follows:

Rotenone was dissolved in chloroform in the proportion of 1 gm. to 3 cc. of solvent. This is added with vigorous shaking to the quince seed and Irish moss mucilage in the proportion desired to make either a 1 or 2% lotion. The mucilage contains 0.1% sodium benzoate as a preservative. If desired, a few drops of perfume may be added.

The applications were tolerated well. There was a temporary cooling, slightly burning sensation from the chloroform contained. Within a few minutes after application the film of lotion dries, and one is then no longer conscious of its presence on the body. Careful observation revealed no subjective or objective ill-effects. Repeated urinalyses remained normal.

**Results in the Treatment of Scabies.** We next proceeded to test the preparation on patients with scabies, prescribing its use according to the following directions:

*First night*—Bathe with hot water and soap, soaking well and scrubbing all over with a stiff brush. Dry. Rub lotion in well over whole body, except face and scalp. Special attention to hands, armpits, waist, nipples and groins.

*Next morning*—Rub lotion in again, without bath. Wear same underwear.

*Next evening*—Rub lotion in a third time, without bath.

*Second morning*—Rub lotion in a fourth time, without bath.

*Following evening*—Bathe thoroughly. Put on fresh underwear, change all bedding, and send to the laundry. Do not apply any more of the medicine, without first returning to the clinic.

The institutional patients were hospitalized during the course of treatment, which was administered by the nurse in charge under the supervision of one of us (E. E. M.). The diagnosis in all cases was made by the finding of typical burrows.\*

It was soon found that immediate relief of itching was obtained even in severely irritated skins, that cure in cases with a light infestation was complete in 2 days, that of severe cases within a week of application. The preparation was tolerated by the most sensitive of skins, and was quite suitable for use in children (7 below the age of 10 in this series). The light infestations, such as were seen mostly in the dispensary, easily responded to the 1% lotion, while

\* One ounce of the lotion is sufficient for a single application to the entire body of an average adult. On this basis the amount of rotenone applied in light infestations is 1.2 gm.; in severe, 4.8 gm. The cost of rotenone crystals averages \$1.00 per ounce in small quantities, and may be obtained from John Powell & Co., 114 East 32d St., New York City.

severe infestation required the 2% lotion for best results, and frequently a second course of treatment for cure. Ten cases in all were treated with the 1% lotion and 14 cases with the 2% lotion, 6 of these being very severe, bedridden, institutional cases with an extensive, pustular dermatitis complicating the picture. The results were most gratifying; there were no treatment failures, and a follow-up examination of the institutional cases (2 to 3 weeks later) showed that cure was complete. Four patients had reinfections. There were no untoward effects detectable in any of the patients, except for moderate dryness of the skin resulting in those who required two courses of treatment. This was easily controlled by the subsequent application of a bland ointment. Urinalyses during and for 2 weeks after the treatment remained normal.

TABLE 1.—DATA ON SCABIES PATIENTS TREATED WITH ROTENONE LOTION.

Initials.	Age.	Sex.	Severity.	Duration.	% Rote- none.	No. of applic.	Day of compl. involu- tion of lesions.	Follow-up 2-3 weeks later.
M. C.	18	F	++	3 mos.	1	8	4th	Cure
B. B.	17	F	++	4 mos.	1	4	7th	Cure
G. N.	10	M	+	3 mos.	1	4	3d	Not followed
H. N.	11	M	+	3 mos.	1	4	3d	Not followed
G. G.	28	M	+	1 year	2	4	3d	Cure
M. G.	27	F	++	1 year	2	4	3d	Cure
B. S.	7	F	+++	3 wks.	2	4	8th	Cure
M. M.	25	F	+	2 days	1	4	4th	Cure
N. H.	10	F	+	3 days	1	4	3d	Cure
B. M.	40	F	++	3 days	1	4	3d	Cure
H. P.	11	F	++	10 days	1	4	3d	Cure
R. A.	35	F	+	2 days	1	4	3d	Cure
B. J.	12	F	+++	2 wks.	2	4	7th	Reinfection 4 wks. later
E. R.	8	F	++++	6 wks.	2	8	7th	Cure
M. T.	69	F	++++	3 wks.	2	8	7th	Reinfection 4 wks. later
B. S.	8	F	++	1 wk.	2	4	3d	Cure
			++++	2 wks.	2	8	10th	Reinfection 2 wks. later
G. L.	8	F	++	1 wk.	2	4	3d	Cure
			++	8 wks.	1	4	4th	Reinfection 3 wks. later
M. A.	28	F	++	3 days	2	4	3d	Cure
D. L.	10	F	++	1 year	2	5	3d	Cure
B. H.	18	F	++++	5 days	2	8	8th	Cure
G. W.	35	F	++++	5 wks.	2	6	7th	Cure
							4th	Cure

We feel on the basis of the results obtained in these 24 cases that rotenone in the form used here is a safe, effective, non-irritating scabeticide.

**Summary and Conclusions.** 1. Rotenone, a constituent of derris root, has been effectively used as a parasiticide in veterinary medicine and agriculture.

2. In the form of 1 or 2% lotions with a base similar to that of many hand lotions (quince seed, Irish moss), it produced prompt

cure of seabies in 24 unselected cases encountered in clinic and institutional practice. At the time treatment was begun, 6 of these patients presented most severe secondary pustular and dermatitic complications.

3. The preparation is non-objectionable from the standpoint of odor, is non-irritating even to sensitive skins, does not stain bed-clothes and underwear, and the patient is not conscious of its presence on the body.

4. Rotenone should be given a more extended trial in the treatment of seabies as well as that of other dermatoses of parasitic origin (*e. g.*, pediculosis, trombidiasis and so on).

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### CRYSTALLINE CONCRETIONS IN THE RENAL TUBULES FOLLOWING SULFATHIAZOLE THERAPY: WIDELY PATENT FORAMEN OVALE IN A PATIENT AGED 77.

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SINCE the acceptance of sulfanilamide and its various derivatives as effective chemotherapeutic agents, reports have appeared in the literature describing undesirable and even fatal complications directly attributable to the use of these drugs. Outstanding among these reports are the references to renal complications associated with the administration of sulfapyridine. Recently sulfathiazole (2-Sulfanilamido-thiazole) was introduced for experimental use reputedly possessing almost equivalent therapeutic action, and being less toxic and less apt to cause the development of undesirable complications. To our knowledge the following case is the first to be reported in which more than transient renal complications have been observed following the administration of sulfathiazole. The case is of further interest because of the discovery at autopsy of a widely patent foramen ovale in a woman of 77. After a brief review of the literature this is the oldest case of this type of congenital cardiac defect on record.

**Case Report.** M. H., a 77-year-old white female, was admitted on Feb. 6, 1940, to the University Hospital with signs and symptoms of bronchopneumonia. Briefly, her history was that of a chronic cough productive of mucoid sputum of approximately 6 months' duration and associated with slight dyspnea on exertion for 3 months prior to admission. There was no history of palpitation, precordial pain or peripheral edema. Two weeks before admission her cough became worse, and she was referred to the hospital with a diagnosis of pneumonia, although there was no history of chills, fever, rusty sputum or pain in the chest. On physical examination she appeared to be an acutely ill old woman, temperature 102.6° F., pulse 100, respirations 36 and blood pressure 110/70. She was propped up in bed and hands and nail beds were slightly cyanotic. The chest was emphysematous with equal but limited expansion. Percussion was impaired over both lower lobes and on auscultation there were medium and coarse moist râles over the same areas with a small patch of bronchial breathing in the third interspace in the left anterior axillary line. The heart was not enlarged to percussion and the apical impulse was palpable in the fourth interspace inside the mid-clavicular line. There were no shocks or thrills. A systolic bruit was audible at the apex which was not transmitted over the precordium. The pulse was full and regular, and there was marked peripheral sclerosis. The abdomen was soft, moderately distended and tympanitic. Peristalsis was hypoaactive. No organs or masses were palpable. No peripheral edema was present.

*Laboratory studies* on admission were as follows: Red blood cells, 4,800,000; hemoglobin 70% and white blood cells 15,600 with 90% neutrophils. The urine had a specific gravity of 1.028, was acid in reaction, there was a trace of albumin, and the sediment was negative. A bedside Roentgen ray showed density of the right lower lobe and the entire left chest. A Type III pneumococcus was recovered from the sputum. Blood culture was negative. Kolmer and Kahn tests were negative.

*Course in Hospital.* A diagnosis of atypical pneumonia was made and sulfathiazole medication started on the day of admission. Three grams were given as the initial dose and the same dose repeated in 4 hours followed by 1 gm. every fourth hour. Digitalis was given in moderate dosage. The patient developed severe and continuous nausea and vomiting which lasted until the sulfathiazole medication was discontinued, at the end of the fourth day. An attempt to combat dehydration was made with daily parenteral administration of solutions of glucose and physiologic saline. In spite of a somewhat lowered temperature and pulse on the fourth day the patient was clinically worse. On the third day, it was noticed that the urine was acid, had a specific gravity of 1.022 and contained abundant albumin.

On the fourth day the specific gravity was 1.019, the reaction acid and there was continued albuminuria plus microscopic hematuria. Although accurate measurements of the urinary output was difficult because of incontinence, the charted output on the fourth day was only 600 cc.—a figure decidedly less than on the 2 preceding days. Sulfathiazole, therefore, was discontinued on the fourth hospital day after a total of 24 gm. had been given. The blood sulfathiazole level on the last day of therapy was 7.2 mg. per 100 cc.\*

On the fifth hospital day, all the urine passed by the patient was obtained by catheter. The amount totalled 160 cc., the specific gravity had fallen to 1.014, reaction was acid, albumin was abundant and there were many hyaline and granular casts.

On the sixth day, the total urine consisted of 225 cc. obtained by catheter. This specimen had a specific gravity of 1.011, was neutral in reaction and

\* Studies in progress would indicate that the present method for estimating sulfathiazole in the blood is unreliable. This given value may be in error by as much as 30%.



contained abundant albumin and many white blood cells. The blood urea nitrogen was 55 mg. per 100 cc. and the blood pressure had risen to 165/85.

On the seventh day, the urinary output was 450 cc. There was moderate albumin and a moderate number of white blood cells. Because the temperature, pulse and respirations were still elevated, 80,000 units of Type III antipneumococcic rabbit serum were given.

On the eighth day the urinary output had risen to 575 cc. and 100,000 more units of Type III antipneumococcic rabbit serum were given. Two days later, on the morning of the tenth hospital day (Feb. 15, 1940), after a short period of apparent improvement, the patient died. Death occurred suddenly and was thought to have been due to coronary occlusion.

Repeated blood counts showed a slowly progressive fall in the number of red blood cells from 4,700,000 on admission to 3,720,000 and 68% hemoglobin on the seventh hospital day. The white blood count varied between 14,000 and 19,000 with 83 to 95% neutrophils. The laboratory data are summarized in the accompanying table.

TABLE 1.—SUMMARY OF LABORATORY DATA.

Date, 1940.	Urine.								Blood.								Chemistry.		
	Amount.	Sp. gr.	Reaction.	Sugar.	Albumin.	Casts.	White blood cells.	Red blood cells.	Red blood cells.	Hemoglobin, %.	White blood cells.	Polymorphonuclears, %.	Lymphocytes, %.	Mononuclears, %.	Basophils, %.	Eosinophils, %.	Bun, mg., per 100 cc. in each case.	Chlorides, mg., per 100 cc. in each case.	Free Sulfathiazole, mg., per 100 cc. in each case.
2/6									4,800,000	73	15,600	90	8	2	0	0			
2/7	Collection started	1.028	Acid	0	±	0	Occas.	0	4,700,000	80	19,200	92	6	2	0	0			
2/8	895+	1.022	Acid	0	+++	0	Occas.	0	4,140,000	77	17,100	90	6	4	0	0			
2/9	600+	1.019	Acid	0	+++	0	Few	Few	4,300,000	79	13,700	84	8	8	0	0		101.2	7.2
2/10	160	1.014	Acid	0	+++	Few granular and hyaline	Occas.	0											
2/11	225	1.011	Neutral	0	+++	0	Many	0									55		
2/12	450	1.009	Acid	0	++	0	Moderate	0	3,720,000	68	17,200	83	10	7	0	0			
2/13	575																		
2/14										65	15,300								

*Necropsy.* Performed 10 hours postmortem. The salient features were as follows: *Kidneys* (160 gm. each) were large and soft. The cortices were narrowed, finely granular and pale reddish-pink in color. Pyramids were large and contained small hemorrhages and prominent grayish-yellow linear streaks of "gritty" crystalline material which converged at the apices and extended into the calices as short, fragile cords. The pelves were thickened,

grossly hemorrhagic and contained deposits of gritty sand-like material. Ureters were negative. Bladder contained a moderate amount of fine sand-like material and the mucosa was reddened. *Heart* (280 gm.) was small. The wall of the right ventricle was thickened and the right auricle was slightly enlarged. The other chambers were not dilated and the valves were normal. The foramen ovale was widely patent (0.8 cm.) and the rim of the foramen was thickened and partially calcified. The secondary auricular septum was absent. The right and left leaves of the primary septum were not fused and resulted in the formation of a "V"-shaped defect in the muscular portion of the atrial septum. This defect, representing the primary ostium, was covered by a thick and fibrous septum. The wall of the pulmonary artery was slightly thickened. *Lungs* were small, heavy (left, 450 gm.; right, 550 gm.), densely fibrous, dark and congested. The external surfaces were finely nodular and "hobnailed" in appearance while the cut surfaces exhibited a dense, diffuse, reticular fibrosis and a marked prominence of the pulmonary arteries. *Liver* (1060 gm.) was small and slightly fatty. *Pancreas* (150 gm.) was soft and flabby and there was moderately extensive pancreatic and peripancreatic hemorrhage with focal areas of fat necrosis. There were large hyperkeratotic plaques on the *cervix* and in the *rectum* there was a large, flat, polypoid mucosal mass.

*Microscopic: Kidneys.* There was slight to moderate fibrous intimal thickening of the small and medium-sized arteries associated with a mild degree of benign nephrosclerosis. There were small focal areas of subacute and healed pyelonephritis with tubular fibrosis, round-cell infiltration and colloid and hyaline casts in adjacent tubules. The collecting tubules were dilated and many were partially to completely obstructed by deposits of crystalline material.\* The intratubular deposits consisted of large and flat, long and blunt and long rectangular crystals. There was fresh hemorrhage into and about the collecting tubules. There was marked fibrous thickening of the subepithelial connective tissue, which was intensely congested, hemorrhagic and infiltrated with lymphocytes, plasma cells and a few neutrophils. Histologically, the *heart* was negative. *Lungs* showed a severe peribronchial and perivascular fibrosis and intense congestion of the septal vessels of the small intervening islands of alveolar tissue. The walls of the pulmonary arteries were thickened. There was a mild degree of bronchopneumonia. The *liver* cells were fatty and there was moderate atrophy and fibrosis of the cells about the dilated central veins. The *pancreas* contained large and small areas of acute degeneration and necrosis of the acinar and islet tissue associated with interstitial hemorrhage and fat necrosis. The *rectal polyp* showed early malignant changes with invasion of the papillary stroma but without invasion of the submucosal connective tissue. The surface of the *cervix* possessed thick plaques of squamous epithelium which were covered with keratinized epithelium. The basement membrane was intact and there was no evidence of malignant degeneration.

**Discussion.** The formation of uroliths following sulfapyridine medication, both experimentally and clinically, has been described by a number of investigators. Recently Plummer and McLellan,<sup>2</sup> and Stryker<sup>4</sup> have summarized the literature and added several new cases. Of particular interest is the fact that the last observer not only found calculi in the calices and pelves of the kidneys and bladder, but also discovered crystalline material in dilated collecting

\* The crystals were seen only in the frozen sections. The crystalline concretions were not seen in the section prepared by the routine paraffin method. In other respects the appearance of the sections was the same.

and convoluted tubules of the cortex. He felt that the site of the occurrence of the crystals resulted from the precipitation of sulfapyridine in these tubules as the urine became more concentrated. It has been our observation that crystalline masses of sulfapyridine occur most frequently in the renal pelves and in the ureters, which suggests that they are most frequently precipitated in urine of maximum concentration, *i. e.*, in the caliceal and pelvic urine.

Following the experimental administration of sulfathiazole to white rats, Gross, Cooper and Scott<sup>1</sup> found that the crystallization of the drug occurred in the distal collecting tubules. These experimental lesions were examined by one of us (D.S.P.) and were identical with those observed in our case. That there should be a greater tendency for thiazole derivatives to recrystallize within the kidney tubules is of interest in view of the statement by Reinhold, Flippin and Schwartz,<sup>3</sup> that their clinical observations suggest that sulfathiazole is not reabsorbed as readily from the kidney tubules as are sulfanilamide and sulfapyridine.

These obvious observations with sulfapyridine and sulfathiazole suggest the etiologic difference for the site of development of the crystalline precipitates. It is our feeling that the site of precipitation is dependent upon the degree of saturation of the drug in the glomerular filtrate, the tubular concentration, and the solubility and (or) reabsorbability of the drug.

Although the death of our patient was probably due to an acute hemorrhagic pancreatitis (of unknown etiology), there can be but little doubt that the oliguria and azotemia played a contributory part, and we believe that these complications were secondary to renal insufficiency resulting from tubular obstruction by the crystalline concretions. Specific tests for the determination of renal function were not performed in this case because the acid urine of high specific gravity and a negative urinary sediment was considered as evidence of adequate renal function. The signs of dehydration and progressive renal failure with the formation of small amounts of dilute urine containing albumin, casts, and red blood cells, which developed in spite of the administration of parenteral fluids, was considered as resulting from the severe and protracted vomiting.

Considering the nature of the renal lesion and the probable etiology, this case clearly illustrates the necessity of an adequate fluid intake and frequent careful urinalyses in determining an uncom-

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#### LEGENDS FOR FIGURES 1, 2 AND 3.

FIG. 1.—Section of kidney showing the deposits of crystalline material in the apical half of a pyramid.

FIG. 2.—Apex of a pyramid with crystalline deposits in the dilated straight collecting tubules and focal areas of interstitial hemorrhage. (Frozen section, 55 X.)

FIG. 3.—Heart showing patent foramen ovale and thickened right ventricle. Dotted lines represent a "Y"-shaped defect in the muscular portion of the interauricular septum which is covered by a thick fibrous membrane.



FIG. 1



FIG. 2



FIG. 3



plicated outcome during a course of sulfathiazole therapy. It is felt that renal complications may even be more frequently seen with sulfathiazole than with sulfapyridine and that a warning with regard to the judicious use of sulfathiazole is indicated. The site of the crystalline concretions of sulfapyridine render them amenable to urologic manipulation or surgical treatment whereas the sulfathiazole concretions must be dealt with indirectly.

The other necropsy findings were incidental, but nevertheless interesting. The widely patent foramen ovale, in a subject 77 years old, with minimal and probably only terminal evidence of myocardial insufficiency, is unique. The etiology of the diffuse reticular pulmonary fibrosis is not clear, but is possibly in part related to a mild, but chronic passive congestion of the pulmonary circuit secondary to an interauricular blood flow with increased filling of the right heart. Other microscopic evidence suggests a chronic low grade bronchitis as an etiologic factor. The moderate atrophy and fibrosis of the central liver cells, in the absence of tricuspid dysfunction, is probably due to a mild, but long standing increase in the right intra-auricular pressure. The malignant polyp in the rectum and the precancerous lesions of the cervix are of but histologic interest.

Washed samples of the crystalline material from both the bladder and renal tubules were analyzed both before and after hydrolysis with hydrochloric acid. The specimens were diazotized and coupled with dimethyl  $\alpha$  naphthylamine. The unhydrolyzed specimens remained colorless, but the hydrolyzed samples turned deep purple. These results were interpreted as indicating that the material from the bladder and renal tubules contained little or no free sulfathiazole but that it was largely composed of a derivative of this drug.

**Summary.** Concretions obstructing the renal tubules and in the pelvis and bladder were discovered at autopsy in a patient following treatment with sulfathiazole. On analysis the material was composed of a derivative of sulfathiazole. The gross and histologic findings in the kidneys were identical with those described by others as occurring in experimental animals. The probable etiologic factors influencing the site of the precipitation of sulfapyridine and sulfathiazole crystals are discussed. Because of the intrarenal precipitation of sulfathiazole it is felt renal complications resulting from the use of this drug may be more serious than those following the use of sulfapyridine. The incidental finding of a widely patent foramen ovale in this 77-year-old woman is unique and to our knowledge is the oldest to be reported.

NOTE.—On April 9, 1940, similar necropsy observations were made at the Philadelphia General Hospital (No. 39070) on a subject from Dr. S. A. Loewenburg's Service.

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## ABSORPTION OF SULPHANILAMIDE AS AN INDEX OF THE BLOOD FLOW IN THE INTESTINE OF MAN.

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THE study of the mechanism for the regulation of the blood flow in the splanchnic area is of both theoretical and practical importance. There is little information, however, concerning the factors which control the blood flow in the splanchnic area in normal subjects. Many of the phenomena occurring in shock and hypertension have been attributed, nevertheless, primarily to changes in the splanchnic circulation.

The mechanisms for the control of the blood flow in the abdominal viscera may not be the type operative in the regulation of the blood flow in the extremities as it is already known that factors which greatly change the blood flow in one tissue (skin) may have little effect in the blood flow in another tissue (muscle).<sup>4</sup>

**Method.** The method devised for the study of the blood flow in the intestine is based on the principle that the rate of absorption from the intestine of an easily diffusible, foreign substance is proportional to the blood flow through the mucosa. Variations in blood flow in the mucosa of the intestine may be studied indirectly by determining the absorption of a readily diffusible substance from the intestine by its appearance time and concentration in the blood. Such an indirect method will not give absolute values for the blood flow in the part of the intestine studied, but it should show changes in the blood flow above or below the basal level. The degree of intestinal motility and the rate of diffusion of the test substance out of the blood stream into the body fluids and urine are not controllable in such a method. Hence the results must be interpreted in light of these limitations.

Sulphanilamide was selected as the test substance because it is freely diffusible in the body tissues, it does not produce local irritation, and its concentration in the blood stream can be determined fairly accurately. The rapid absorption of sulphanilamide when it is placed in the small intestine indicates that it is absorbed directly into the blood stream. It was assumed that an increase in blood flow to the intestine above the basal rate would be reflected by a more rapid absorption of the sulphanilamide, while a decrease in blood flow below the basal rate would result in a slower absorption

of sulphanilamide. No attempt was made to establish the rate of sulphanilamide absorption in a large series of normal subjects. An experiment on each subject under basal conditions served as the control.

All subjects were in the basal state. No fluid was given after 9 P.M. the night preceding the experiment. A 1% solution of sulphanilamide at 38° C. (200 to 300 cc.) was injected directly into the small intestine through a Rehfuß tube which had been passed into the second portion of the duodenum. The position of the tube was ascertained by fluoroscopy. The subjects were trained to swallow the tube and they experienced no nausea throughout the procedure. Blood was collected from the antecubital vein at 2- to 3-minute intervals for at least 20 minutes and then samples were taken at 5- to 10-minute intervals for 1 to 2 hours. In experiments in which the subjects were tilted upright the blood was drawn from the femoral vein.

In a second series of experiments in which changes in the blood flow in the colon were investigated, 300 cc. of a 1% solution of sulphanilamide at 38° C. were given by rectum. These subjects received a cleansing enema at 11 P.M. the night before the experiment. Blood samples were collected from the antecubital veins.

Both free and total sulphanilamide were determined on whole blood by the method of Marshall and Litchfield<sup>5</sup> using the Evelyn colorimeter.<sup>1</sup> As the total sulphanilamide closely paralleled the free sulphanilamide, only the levels of the free sulphanilamide have been recorded in the charts.

**Results.** *Sulphanilamide in the Small Intestine.* A 1% solution of sulphanilamide (300 cc.) was given by duodenal tube to 2 normal subjects and to 1 subject with postural hypotension. The subjects weighed 170, 190 and 159 pounds, respectively. The 300 cc. were given in 1.5 to 3 minutes. Figure 1 shows the free sulphanilamide level in the blood in these 3 subjects. In 10 to 13 minutes the sulphanilamide concentration reached its peak of 6.7, 8.7 and 6.9 mg., respectively, at the end of 2 hours it was between 4 and 5 mg. per 100 cc. Two hundred cubic centimeters of a 1% solution of sulphanilamide were given by duodenal tube to 2 normal subjects who weighed 100 and 150 pounds, respectively. The sulphanilamide concentration reached 5 mg. per 100 cc. in 10 and 20 minutes, respectively. At the end of an hour the concentration was still approximately 5 mg. per 100 cc.

In order to determine whether the blood flow in the small intestine was decreased by shunting blood to the skin, one of the normal subjects was placed in a fever cabinet and the rectal temperature was raised to 103° F. The subject was then given the same amount of sulphanilamide by duodenal tube. The concentration of the sulphanilamide in the blood was slightly but not significantly higher than in the control experiment.



In order to determine whether the blood flow in the small intestine was decreased by venous pooling in the dependent portion of the body, the subject with postural hypotension was given 300 cc. of a 1% solution of sulphanilamide by duodenal tube while he was standing at an angle of  $60^\circ$  (Fig. 2). On standing, his blood pressure fell from the resting level of 110 mm. systolic and 70 mm. diastolic to a "shock level" of approximately 60 mm. systolic and 50 mm. diastolic. The heart rate rose from 56 to 90 beats per minute. The sulphanilamide level in the blood, in spite of the considerably decreased systemic blood flow, rose as quickly under these conditions as it had when it was administered in the horizontal position.

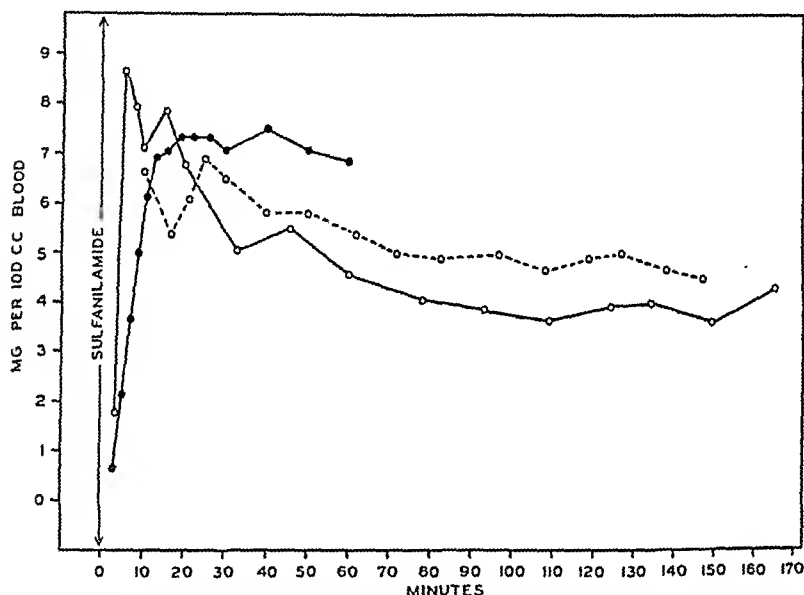


CHART 1.—Concentration of sulphanilamide in blood in mg. per 100 cc. after the administration of 300 cc. of a 1% solution of sulphanilamide by duodenal tube to 3 subjects under basal conditions.

One cubic centimeter of pitressin was injected intramuscularly into 3 normal subjects and sulphanilamide was given as before by duodenal tube (Fig. 3). In 2 cases the control sulphanilamide curve and the sulphanilamide curve after pitressin were nearly identical. In the third case, the sulphanilamide concentration in the blood was somewhat greater after pitressin than before.

*Sulphanilamide in the Colon.* Three normal subjects were given 300 cc. of a 1% aqueous solution of sulphanilamide at  $38^\circ$  C. by rectum. The concentration of the drug in the blood stream rose much more slowly than when it was administered by duodenal tube. At the end of  $1\frac{1}{2}$  hours the level in the blood was between 2.5 and 4 mg. per 100 cc. and it was still slowly increasing. When the experiments were repeated on these same subjects after the intramuscular injection of pitressin, the sulphanilamide appeared

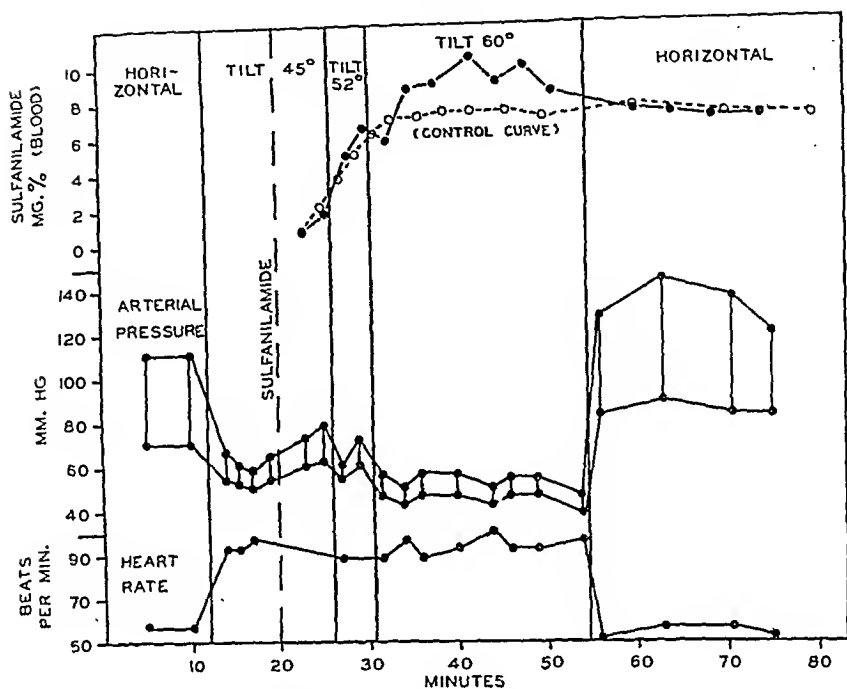


CHART 2.—The effect of postural hypotension on the absorption of 300 cc. of a 1% solution of sulphanilamide from the small intestine. Dotted line is the concentration of sulphanilamide in the blood in the control experiment which was performed with the subject in the horizontal position; solid line is the concentration of sulphanilamide in the same subject whose blood pressure has been lowered by tilting.

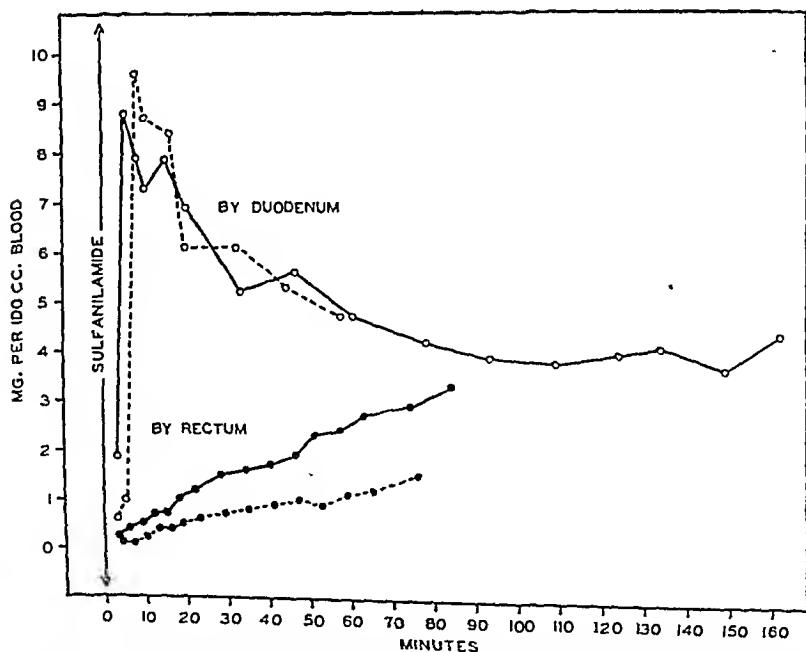


CHART 3.—The effect of the intramuscular administration of 1 cc. of pitressin on the absorption of 300 cc. of a 1% solution of sulphanilamide from the small and the large intestines. The pitressin was injected 10 minutes before the sulphanilamide was given. The solid line=control; dotted line=after pitressin. Pitressin had no effect when the sulphanilamide was given by duodenum, but it caused slower absorption when the sulphanilamide was given by rectum.

later in the blood and the concentration in the blood increased more slowly (Fig. 3).

**Discussion.** When variations in blood flow to the small intestine are studied by the absorption of an easily diffusible substance, it is essential that the test substance be placed directly in the small intestine. Otherwise, changes in emptying time of the stomach will greatly modify the results. This is particularly true when collapse is induced, because nausea is a frequent symptom of the collapse and is accompanied by dilatation of the stomach and closing of the pylorus.

When a solution of sulphanilamide is introduced into the small intestine, it appears in the blood in a relatively high concentration in a short time. At first it was thought that this probably indicated that the sulphanilamide was easily diffusible and that there was a high basal blood flow in the small intestine. A second possibility was, however, that the high concentration of the sulphanilamide in the small intestine and its rapid diffusion were sufficient to account for the blood levels obtained, and that the basal blood flow in the small intestine was slight. In a study of the blood flow of this nature it is essential to decide whether the resting blood flow is great or small. This is axiomatic because the vasoconstrictor effect of certain stimuli or drugs will be overlooked unless vasodilatation is present in the tissue when the control observations are made. Thus it is easy to overlook the vasoconstrictor effect of epinephrin on the digital vessels if the hand is already cold when the drug is injected. Likewise, if the vessels are already dilated when the observations are begun, stimuli which are capable of producing vasodilatation may seem to have little effect. Hence, arterial occlusions produce little reactive hyperemia in the skin when the vessels are already widely dilated by local heat.

On the assumption that under the conditions of the experiment the rapid appearance of sulphanilamide indicated a fairly rapid blood flow in the small intestine, attempts were made to reduce the blood flow. The shunting of a portion of the blood to the skin by heating the body had no effect on the rate of sulphanilamide absorption from the small intestine. Likewise, in dogs it has been shown<sup>3</sup> that the resting blood flow through the superior mesenteric vessels is not decreased by exercise. Thus it appeared that the basal blood flow in the small intestine was so low that when additional blood was needed for heat dissipation or exercise, it was not obtained by decreasing the blood flow in the small intestine.

The postural experiment in which the mean arterial pressure was lowered again indicates that the basal blood flow to the small intestine is low. When the mean blood pressure was lowered, the absorption of the sulphanilamide was still rapid. The blood flow to areas with a large blood supply usually decreases as the blood pressure falls. In the hand with the vessels widely dilated by local

heat the blood flow falls for two reasons: 1, reflex vasoconstriction; 2, fall in pressure head. Smith<sup>6</sup> has shown that the blood flow through the kidney, an organ in which the resting blood flow is high, is reflexly decreased when blood is pooled in postural experiments even though the mean arterial pressure does not fall. However, in organs in which the resting blood flow is low it is not possible to predict exactly what effect postural hypotension will have on the blood flow for, as the vessels are already constricted, it is much easier for them to compensate for a drop in pressure by a slight degree of vasodilatation than it is for organs in which vasodilatation is already present.

The experiments with pitressin indicated that it had little effect on the blood flow to the resting small intestine. In the colon, on the other hand, pitressin definitely slowed the absorption of the drug. It is difficult to say whether this was the result of direct vasoconstriction or whether the vasoconstriction was produced by clamping off of the vessels in the wall of the colon during the periods of increased peristalsis caused by the pitressin. Animal experiments, in accordance with observations on man here reported, indicate that pitressin has a more powerful action on the colon than on the rest of the intestinal tract.<sup>2</sup>

At the onset of this study it was felt that a decreased blood flow to the small intestine in cases of shock might explain some of the variations in absorption of sulphanilamide and sulphapyridine which are frequently observed in patients. However, in postural collapse sulphanilamide enters the blood stream rapidly and a satisfactory blood level is obtained despite the increased venous pooling and fall in blood pressure. It is probable that shock adversely affects the absorption of the drug chiefly by prolonging the emptying time of the stomach rather than by interfering with the absorption of the drug once it has reached the small intestine.

**Summary and Conclusions.** 1. The blood flow in the human intestine has been investigated by determining the appearance time and the concentration curve in the blood of free sulphanilamide when a known amount of sulphanilamide in solution is introduced directly into the small intestine or colon.

2. Under basal conditions a blood level of 6 to 8 mg. per 100 cc. of free sulphanilamide was obtained in 10 to 13 minutes when 300 cc. of a 1% solution of sulphanilamide were placed in the duodenum.

3. Heating the body or inducing collapse in a subject with postural hypotension did not alter the curve of sulphanilamide in the blood. This is interpreted as indicating that the basal blood flow to the small intestine was low and that the rapid appearance of sulphanilamide in the blood was the result of its rapid diffusion.

4. Under basal conditions sulphanilamide was absorbed much more slowly from the large bowel. When 300 cc. of a 1% solution

of sulphanilamide were given rectally the blood level rose to between 2.4 and 4 mg. per 100 cc. at the end of  $1\frac{1}{2}$  hours.

5. Pitressin failed to influence the rate of absorption of sulphanilamide when the substance was given by duodenal tube. Pitressin caused a delay in absorption when the sulphanilamide was placed in the large bowel.

6. The rapid absorption of the sulphanilamide in the collapse induced by the upright position in a subject with postural hypotension suggested that even in shock sulphanilamide diffuses so rapidly that it is adequately absorbed once it is present in solution in the small intestine. Dilatation of the stomach and closure of the pylorus may, however, prevent the drug from reaching the small intestine.

The determinations of the sulphanilamide concentration were done by Miss Sophia M. Simmons, B.S.

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## THE VITAMIN A STATUS OF FAMILIES IN WIDELY DIFFERENT ECONOMIC LEVELS.\*

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As part of a study in which the nutritional status of 100 families of widely varying cash incomes was investigated concurrently with food intake,<sup>7</sup> photometric measurements were made on all persons of 6 years of age or older in the various families, for the purpose of relating their response to this test with vitamin A intake. Other comparisons also were made, including the relationship between response to the photometric tests and cash income, money spent for food, and education of the various families.

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The data of this paper were taken from a dissertation submitted by the junior author, Agnes Pauline Sanders, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Home Economics, under the direction of the senior author, Pauline Beery Mack, who is Director of Research in Home Economics at the Pennsylvania State College.

A total of 418 individuals in 100 families was included in the study, of which 327 persons were sufficiently old to take the photometer tests.

**Photometric Procedure.** The investigation was carried on from July, 1935, to August, 1937, as part of a long-time study on the dietary habits and nutritional status of representative Pennsylvania families. When the work was begun, no instrument specifically designed to measure darkness adaptation in relation to vitamin A status was available. Jeans and Zentmire<sup>4a,b</sup> had described the use of an electrically illuminated Birch-Hirschfeld photometer, not originally made for this purpose, in the clinical examination of subjects for moderate degrees of vitamin A deficiency. The method suggested by these authors was adopted in this study, and members of 81 of the families were tested by the Jeans technique.

The remaining 19 families were examined by means of the biophotometer, first described by Jeans, Blanchard, and Zentmire.<sup>5</sup> These families were distributed throughout the various cash income groups.

The use of the Birch-Hirschfeld photometer as an instrument for evaluating darkness adaptation has been described by Jeans and Zentmire,<sup>4a</sup> by Bigwood,<sup>1</sup> and by Mack and Smith.<sup>7</sup> Two tests were made with the subjects by the use of the Birch-Hirschfeld photometer after the method of Jeans, the first test after the subject had looked for 5 minutes at a white screen placed at a standard distance in front of him, and illuminated by a 200-watt Mazda lamp behind his back and shining over his shoulders, and the second after a 10-minute subsequent period in darkness. In preliminary trials made before the study of the family members was begun, it was found that the test following bright light exposure should be made at a precise time after exposure, because ability to see changes rapidly when a subject has been placed in darkness immediately after bright light exposure. A time of between 20 and 25 seconds was chosen for taking this test, and the time was judged with a stop-watch which was started at the same instant as the room was darkened for the test.

Since no calibrations in terms of light intensity were furnished with the Birch-Hirschfeld photometer, but merely the transmission of the wedge, the instrument was calibrated for every combination of wedge and iris setting by means of a Weston Photronic Cell No. 594, fitted with a Corex Visual Correction Color Filter, using the method of Fogle.<sup>3</sup> The calibration was accurate within the limits of the method of procedure—this was made on the entire glass field over which the plate bearing the five circular openings was placed during the test. The luminosity of the center dot was then calculated on the basis of the comparison of the area with the whole field. This introduced a slight error in that the rate at which the light changed over the entire area, as the iris was opened or closed, was different from that at which the intensity of the small center dot was changed. The center dot could not be used alone in the calibration, however, because it did not transmit sufficient light to be recorded when focused on the photoelectric cell of the calibrating device.

When the biophotometer was substituted for the Birch-Hirschfeld instrument, readings were taken with the new instrument: (a) upon entry of the subject into the darkroom in which the tests were given; (b) after a 10-minute period of rest in the darkroom; (c) after a 5-minute exposure of the subject's eyes to light shining through a luminescent screen within the instrument, the test in this instance being made between 20 and 25 seconds after the close of the exposure interval, and (d) after 2½-, 5-, 7½-, and 10-minute periods of subsequent darkness adaptation. The only results given in the present report, however, are those corresponding to the tests of the

older instrument, namely, the test after 5 minutes of bright light exposure, and that following the 10-minute subsequent period in darkness.

As mentioned previously, the members of the 19 families tested with the biophotometer were scattered throughout the socio-economic range. Whether the results obtained with the 81 families with whom the older instrument was used were analyzed separately, or whether the data for all 100 of the families were considered as a whole, the same positive correlations between response to the test and family intake of vitamin A were obtained.

*Method of Determining Vitamin A Intake.* The unit composition of each family was ascertained by the method of Stiebeling and Phipard.<sup>9</sup> This consisted, in brief, of calculating from the number of meals eaten at home by the different members of the family during the week the equivalent in terms of the number of unit persons eating at home for seven 3-meal days during the week. The average content of the diet per unit person in each family was then determined by dividing the average total weekly vitamin A content of the family diet by the family equivalent in unit persons eating 21 meals, or 3 meals a day for 7 days, at home during the week. This gave the vitamin A intake per unit person per week, for each of the 100 families. The quotient obtained by dividing this by 7 was the average vitamin A intake per unit person per day. The vitamin A content of the diet is reported in international units.

The weekly vitamin A intakes of the families may be regarded as estimated vitamin A intakes, since they were calculated from tables of average food values based on analyses of investigators of recognized standing, although samples of the family dietary were not themselves analyzed for vitamin A content in this study. The dietary records used in the calculations consisted of grocery slips, company books, and housewives' tabulations of amounts of various foods served and discarded. Total family intake only was recorded—no attempt was made to record the food eaten by individual family members because of limited personnel available for assistance in the study. The family was visited from two to six times throughout the period of record-keeping by one of the authors. The family dietary intake was kept for a 3-month period for the first 40 families. After the data from these records were analyzed, it was found that little variation occurred from week to week during the time covered, which was continuous within one season of the year. For the remaining 60 families, records were kept for a 2-week period only.

Seasonal distribution of families studied was such that some families from each income group were analyzed at each of the various times of the year. Because the photometer tests and the food intake were recorded for identical periods of the year for each family, comparisons between response to the former test and vitamin A intake are considered altogether appropriate.

*Methods of Reporting Cash Income and Educational Ratings of Families, and Amounts Spent for Food by Families per Unit Person per Meal.* The families are reported as having Cash Income Rating 1, if they had annual incomes ranging from \$20,000 to \$5,000 annually; Rating 2, from \$4,999 to \$2,500; Rating 3, from \$2,499 to \$1,000; Rating 4, below \$1,000, but not on direct relief; Rating 5, on direct governmental relief.

The arbitrary educational ratings to which the families were assigned were as follows: Educational Rating 1 was given to those families in which all adult members (persons 19 years of age or over who were not continuing their education) were college graduates, one or more with a Ph.D. degree; Rating 2, to those in which all adults were college graduates, one or more with a master's degree; Rating 3, to those in which all adults were college graduates with a bachelor's degree; Rating 4, to those in which one adult was a college graduate; Rating 5, to those in which all adults had had some

special training beyond high school (nurse's course, trade school, or other non-college training beyond high school); Rating 6, to those in which all adults were high school graduates, at least one with some special training beyond high school; Rating 7, to those in which all adults were high school graduates; Rating 8, to those in which at least one adult was a high school graduate; Rating 9, to those in which at least one adult had passed the eighth grade; Rating 10, to those in which none of the adults had passed the eighth grade.

In resolving the families to a common basis with respect to the amount spent for foods of various types, the unit-person content of each family was computed from a scale of comparative food costs for persons different in sex, age, and activity, in which the expenditure for food of a moderately active man of the same description as was used in establishing arbitrary, relative nutrient-requirement standards was taken as the unit. As a means of calculating comparative expenditures for different individuals, the scale of relative food-expenditure values suggested by Stiebeling and Phipard<sup>9</sup> was used; this was based upon dietary studies made at the U. S. Bureau of Home Economics.

**Results of the Study.** *Correlation Between Photometer Tests and Vitamin A Intake.* In relating the bright light test and the darkness regeneration test to vitamin A intake for the entire 100 families, irrespective of the arbitrary sub-groups later described into which each fell, it was found that the correlation coefficient was  $+0.57$ , with a probable error of  $\pm 0.0454$ . Since the coefficient of correlation was more than 6 times its probable error, it was considered significant. The correlation coefficient of the darkness regeneration factor as related to the vitamin A intake of the entire 100 families was  $+0.57 \pm 0.0454$ , also a significant correlation.

When the bright light factor was related to the darkness regeneration factor for each of the 100 families, a correlation coefficient of  $+0.85 \pm 0.019$  was found, which indicates a highly significant correlation.

In establishing a definite correlation between the vitamin A intakes of families of various dietary habits and their responses to a photometric test, the authors confirm the early work of Jeans and Zentmire<sup>4a,b</sup> with the Birch-Hirschfeld photometer, and that of Jeans, Blanchard, and Zentmire<sup>5</sup> in their introduction of the biophotometer, and of their findings by the use of this instrument with orphanage children; of Jeghers,<sup>6</sup> who studied responses of medical students to a biophotometer test in relationship to their dietary habits, and who produced vitamin A deficiency in an experimental subject and noted the progress of the deficiency and its recovery by means of a biophotometer; and of Maitra and Harris<sup>8</sup> who used the Birch-Hirschfeld instrument in studying the vitamin A status of London and Cambridge school children and noted their favorable response to vitamin A therapy as shown by improvements in tests with this instrument.

*Comparison of Vitamin A Intake of Families in Different Arbitrary Groups of Responses to Photometer Bright Light Test.* The families were divided into three arbitrary groups with respect to average



response to the photometer test following bright light exposure. This division was made on the basis of the range of average response of the families to the test, and without reference to assumed normal or abnormal responses.

The first, or best group (hereinafter designated as Group I) was composed of 14 families, in which the average family light requirement constituting the end-point of persons of 6 years of age or over was 0.6 millifoot candles or less. The second group (Group II) included 45 families, the members of which required from 0.7 to 5.0 millifoot candles to observe the end-point when taking the test following bright light exposure. The third group (Group III), or that in which the poorest response to this test was shown, included 41 families averaging over 5.0 millifoot candles as their end-point. The relationship of the average responses of the three groups of families, separated as to their average bright light factor, to vitamin A intake, to the average darkness regeneration factor, to average annual cash income, to the average amount spent for food per unit person per meal, and to the family educational rating are shown in Chart 1.

The statistical method of Fisher<sup>2</sup> was used to compute the probable significance of the differences between the average vitamin A intake per unit person per day in the families of the three bright light factor groups. In this analysis, the comparisons of vitamin A intake were based on the average vitamin A intake per unit person for each family; the mean photometer test of the different members of the family who were given the test was used as the basis for classifying the families into the respective groups. It was found by this statistical procedure that the odds are greater than 100 to 1 that the difference is significant between the vitamin A intake of families taking the best photometer test with respect to the bright light response (Group I, giving a bright light test of 0.6 millifoot candles or less) and that of families in the second best group on the basis of this test (Group II, having a bright light factor from 0.7 to 5.0 millifoot candles, inclusive)—obviously a highly significant difference. Furthermore, there was a high degree of significance—odds were more than 100 to 1—of the difference in vitamin A intake between families of Group I and Group III, the latter including families averaging more than 5.0 millifoot candles in the bright light test. The difference in average vitamin A intake per unit person per day was not significant between Groups II and III, when the families were grouped on the basis of the bright light factor. The average vitamin A intake per unit person per day in the three groups was found to be 16,482 international units for Group I with a standard error of  $\pm 2,104$ ; 10,775 for Group II with a standard error of  $\pm 1,174$ ; 9,984 for Group III with a standard error of  $\pm 1,031$ .

At first glance, the average vitamin A intake per unit person

seems high for all three of the groups classified by the photometer's bright light factor, particularly for the poorest group, since the average for this group is higher than various of the tentative requirements which have been suggested by different investigators for a unit person of the same specifications as were used in this study. It must be considered in this connection, however, that all of the family averages within any one group were not the same as the group average, and that the minimum family vitamin A average intakes

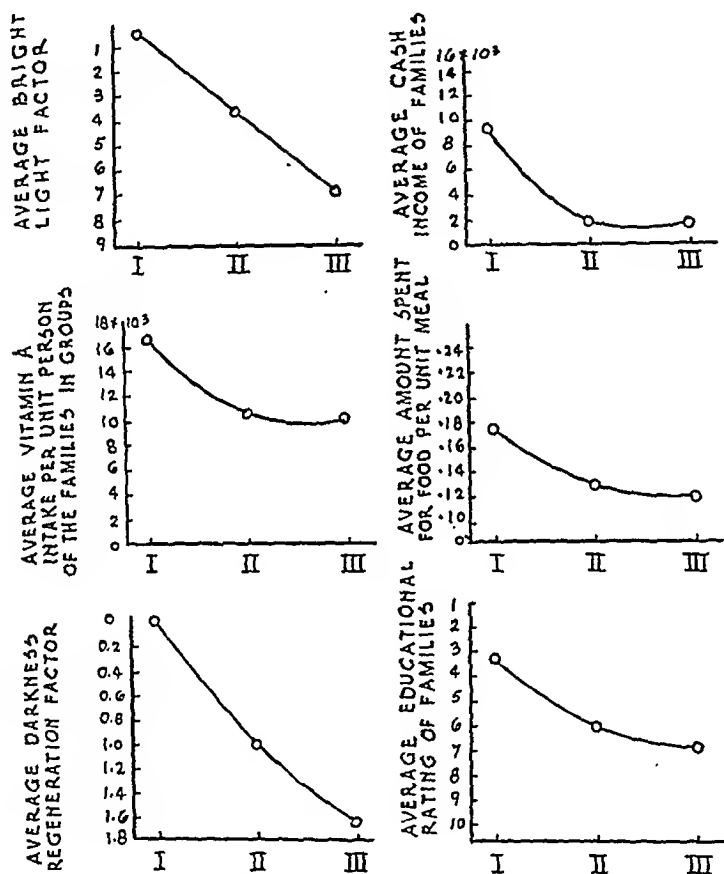


CHART 1.—Vitamin A intake per unit meal (per unit person per meal), response to photometer tests, cash income, money spent for food, and education of families grouped according to response in bright light tests.

in the three groups were 8,180, 1,052, and 1,954 international units per person per day, respectively. It must be remembered further that any excess of vitamin A consumed by some of the families of one of the arbitrary groups was of no value to any of the families in this group receiving a lesser amount of this nutrient. None of the averages of vitamin A, therefore, are to be regarded as necessarily desirable amounts of this dietary component.

The three family groups, separated with respect to their response to the photometer test after bright light exposure, are graphed in

Chart 2 as to their comparative vitamin A intakes per unit person. From this it is shown that the majority of the families in Group I received 12,000 or more international units of vitamin A per unit person per day, whereas no family averaged below 8000 units. In Group II, more than three-fourths of the families received less than

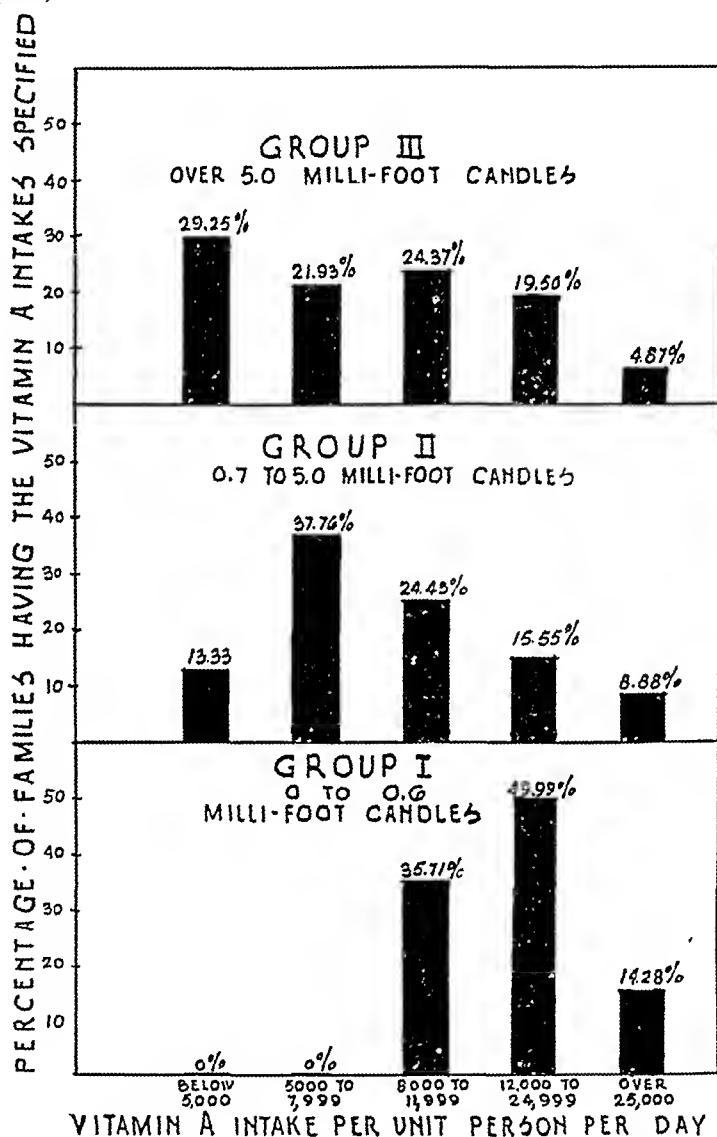


CHART 2.—Percentage distribution of families as regards vitamin A intake, grouped according to the bright light factor. Group I included families giving the best and Group III the poorest average responses to this part of the photometer test.

12,000 units, daily, and more than half of the families received less than 7999 international units of vitamin A per unit person per day. In Group III, a larger percentage of the families had vitamin A intakes less than 5000 units than did the other groups, and more than three-fourths of the families received less than 12,000 units daily.

The apparently large consumption of vitamin A by some of the families in the lower groups of response to the bright light photometer test may be accounted for either by the fact that tables of averages from which the vitamin A values of the dietaries were calculated may not account for some of the losses in vitamin A content of foods from various causes, such as conditions of production, of storage, or of preparation, or by the fact that variations undoubtedly are to be found in the utilization of this vitamin by different individuals.

The uniformity among the various family members with respect to their response to the bright light test is interesting. In Group I, all of the members of 85% of the families were within the group limits of this test, with only one member of each of the remaining families found in the group next below that of the family average. In Group II, all of the members of 42% of the families were found within the limits of the group as a whole, while 30% of the families had one member in the class next below that of the group, 11% had one member in the class next higher, 11% had more than one member in the class next below that of the family average, and 2% had more than one member in the class next above that of the group in which the family average with respect to this test was found. In Group III, only 26% of the families had all of their members within the group limits, while the remainder had one or more family members in the other photometer response groups. Thus, a high degree of uniformity of response to this test was found in members of families giving a high response to the test, with a progressive decrease in uniformity as the average family response to the test became lower.

*Comparison of Vitamin A Intake of Families in Different Arbitrary Groups of Response to Photometer Darkness Regeneration Tests.* The families were divided into three classes on the basis of their average response to the darkness regeneration tests; the divisions were based approximately on the range of responses of the families in the groups with respect to the bright light tests. The first group consisted of families of which the average darkness regeneration test was 0.05 millifoot candle and under. The second group had average tests ranging from 0.06 to 0.9 millifoot candles, inclusive, and the third group, over 0.9 millifoot candles. There were 18 families in the first, 31 families in the second, and 51 families in the third group. Sixty-nine of the families fell in the same respective groups in the two tests, and 31 of the families fell in one group lower or higher with respect to the darkness regeneration test than they did in the test following bright light exposure.

In Chart 3 there is shown the average response to the photometer tests, the average vitamin A intake per unit person, and the averages for the three socio-economic factors—cash income, amount of money spent for food per unit person per meal, and average

family educational rating—when the families were grouped into the three photometer darkness regeneration groups. The vitamin A intake of the families of Group I was 14,307 international units per unit person per day, with a standard error of  $\pm 1,931$  units; that of the families of Group II was 11,999, with a standard error of  $\pm 1,521$ ; and that of Group III was 9,714, with a standard error of  $\pm 984$  international units.

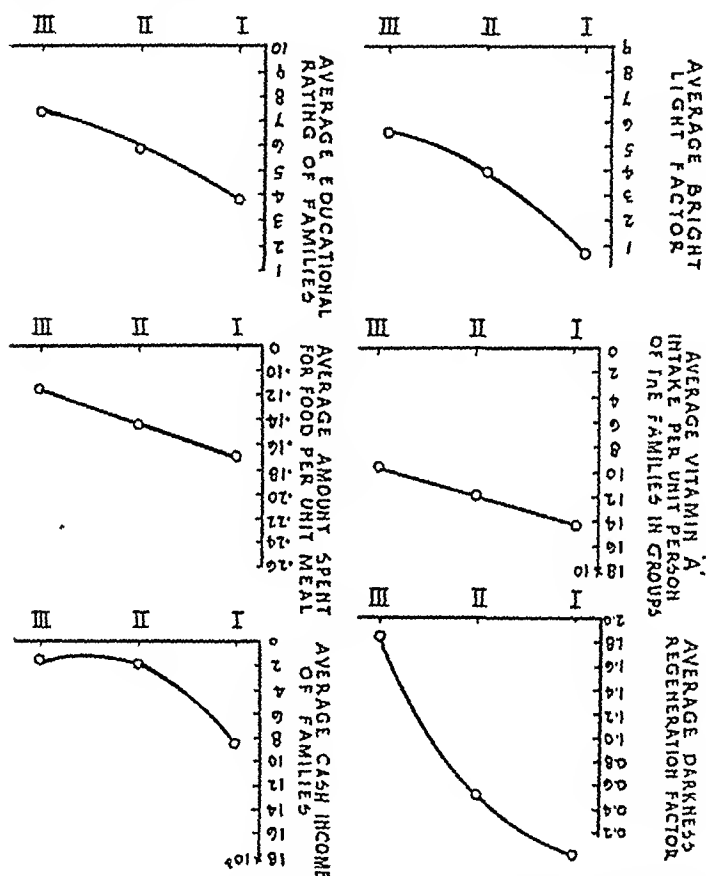


CHART 3.—Vitamin A intake, response to photometer tests, cash income, money spent for food per unit meal (per unit person per meal), and education of families grouped according to response in darkness regeneration tests.

Again using the method of Fisher,<sup>2</sup> it was found that the difference between the average vitamin A intake per unit person per day of the families of Group I (the highest with respect to the darkness regeneration factor) and that of the medium group (Group II) with respect to vitamin A intake, and that between Groups II and III were not significant. The difference between the best and the poorest groups (I and III), however, was found to be highly significant, by odds greater than 100 to 1.

The distribution with respect to vitamin A intake of the families within each darkness regeneration group is shown graphically in

Chart 4. In this figure it is seen that the families are more widely scattered throughout each of the groups than was the case with the groups based on the bright light test. In common with the bright light response groupings, however, there is a tendency for percentages of families in the lower vitamin A consumption sub-

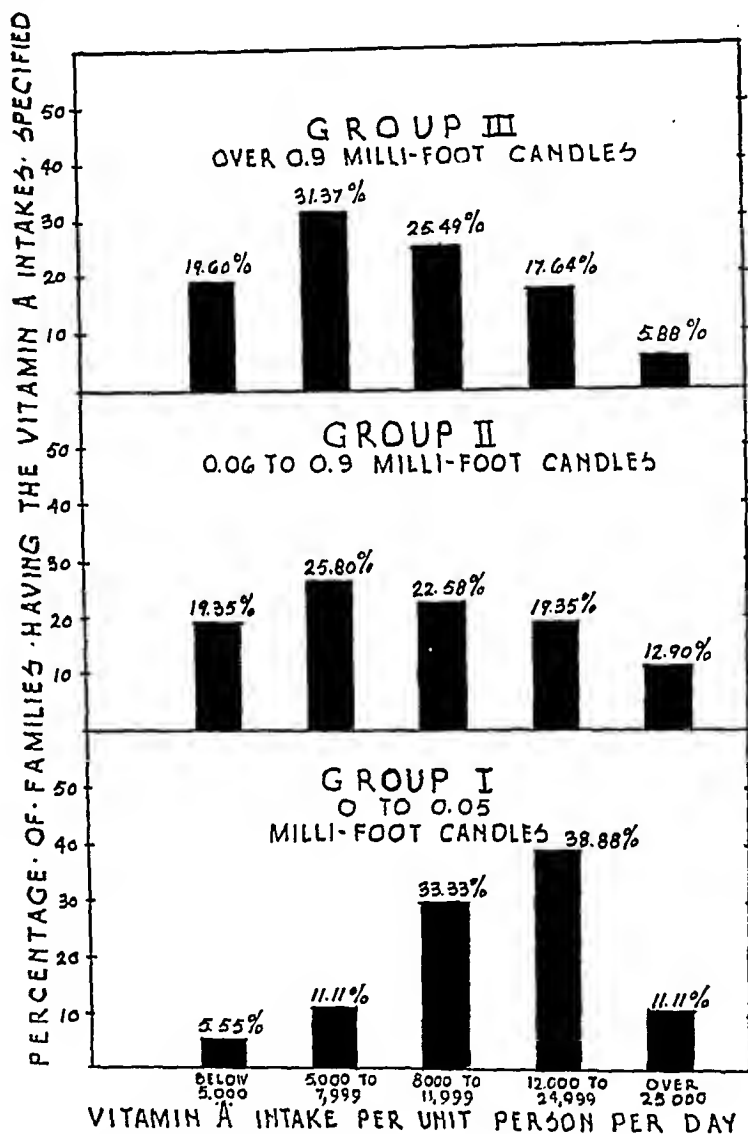


CHART 4.—Percentage distribution of families as regards vitamin A intake, grouped according to the darkness regeneration factor. Group I included families giving the best and Group III the poorest average responses to this part of the photometer test.

divisions to become progressively larger and those in the higher vitamin A intake sub-groups to become progressively smaller from Groups I to III.

*Relationship Between Response to Photometer Tests and Cash Income, Money Spent for Food, and Educational Ratings of Families.*

It is apparent from Chart 1 that there is a relationship between the average responses of the families in the study to the bright light test and their cash incomes, the money which they spent for food, and their educational ratings. The highest group on the basis of this test consisted of families averaging \$9,307 a year; the second group \$1,907; and the lowest \$1,713, with average income group ratings of 1.3, 3.1, and 3.7, respectively. The amount spent for raw food per unit person per meal ranged from \$0.179 in the highest bright light photometer response group to \$0.121 in the lowest. The educational rating of the highest group was 3.3, that of the next group was 6.0, and that of the poorest was 6.8.

A calculation of the percentage distribution of the families with respect to education of adult members showed that all of the families in Group I with respect to the bright light test were in the first two classes educationally. About half of the families in the second of the bright light groupings were in the lowest educational class, with the other half scattered through the other classes. In the poorest bright light group 63% of the families were in the lowest educational class, with the remainder scattered through the other four classes. Similar results were obtained by comparing the financial and educational status of the families with their response to the darkness adaptation part of the photometer test.

Although cash income, food expenditure, and educational status are undoubtedly closely associated with each other and with a choice of diet, unpublished data from the laboratory of the authors have shown that higher food expenditure and better education rating of the adult members of a family are independently related in a causal manner with a good selection of foods.

**Summary.** Definite relationships have been shown between the average vitamin A intake in the diet per unit person and the response to photometer tests of members of 100 Pennsylvania families. Cash income, money spent for food, and the education of adult members of the family have been shown to be related to the vitamin A consumption of the family, and to the consequent response of family members to the photometer test.

If the highest type of response to the photometer test as given in this study is to be regarded as desirable, as is generally assumed, the study points to the fact that many families, particularly those in the lower socio-economic groups, are not selecting foods with a satisfactorily high vitamin A content. The study indicates further that a larger estimated vitamin A content of the diet per unit person (as calculated from food analysis tables) may be needed than is generally recommended, if the best darkness adaptation results are to be achieved.

Although a few of the families in the poorer groups (classified on the basis of response to the darkness adaptation tests) were receiving 12,000 international units of vitamin A or more per unit

person daily, the greater majority were receiving less than this amount and almost half were receiving less than 8000 units. Moreover, no families receiving less than 8000 international units of this vitamin were in the highest class with respect to the bright light test, and few were receiving less than this amount who were in the best class on the basis of the darkness regeneration test. In other words, poor darkness adaptation is apparently possible with high vitamin A intake (as calculated from dietary records), whereas good response is not possible with a low intake.

Good average responses to the photometer tests were associated not only with uniformly high intakes of vitamin A, but with a greater degree of uniformity of response to the tests throughout the members of a certain family, a situation which is characteristic of biologic material in general in which a greater uniformity is found the more nearly an optimum condition is achieved with respect to a certain factor.

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## THE RELATIONSHIP OF THE DIETARY INTAKE OF NICOTINIC ACID TO THE COENZYME I CONTENT OF BLOOD.\*

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THE widespread occurrence of Coenzyme I (diphosphopyridine nucleotide) and Coenzyme II (triphosphopyridine nucleotide) in animal tissues and the prominent rôle played by these substances in many metabolic processes have been repeatedly demonstrated. These coenzymes function as carriers in numerous oxidative systems which involve the transfer of hydrogen from metabolite

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through a series of intermediate stages to molecular oxygen. The nicotinic acid amide portion of the coenzyme molecule may be reversibly oxidized and reduced and serves as the site of hydrogen transport. The possible rôle of Coenzyme I in phosphorylation processes further accentuates the importance of these compounds in cellular metabolism.

The importance of nicotinic acid and certain of its derivatives in bacterial nutrition has been established by Knight,<sup>10</sup> Mueller,<sup>14</sup> Koser *et al.*,<sup>13</sup> and Fildes.<sup>6</sup> Elvehjem *et al.*<sup>4</sup> have shown that nicotinic acid is the specific cure for the characteristic "black tongue" syndrome observed in dogs fed the Goldberger diet. The importance of this vitamin in the nutrition of the monkey and pig has since been recognized.<sup>3,9</sup> Finally, the relationship of nicotinic acid to human pellagra has now been abundantly demonstrated.<sup>7,8,16,17</sup>

The fact that nicotinic acid amide is a constituent of the pyridine nucleotides has led to the logical assumption that at least one of the functions of nicotinic acid in the organism is to serve as a component of the coenzyme molecule. Such a relationship has been observed in the case of bacteria by Knight<sup>10</sup> and Fildes,<sup>6</sup> and in the higher animals by Axelrod, Madden, and Elvehjem.<sup>2</sup> The latter authors demonstrated a decrease in the Coenzyme I content of the liver and muscle of both the dog and the pig in an uncomplicated nicotinic acid deficiency. Vilter, Vilter, and Spies<sup>18a,b</sup> noted a decrease in the Factor V (Coenzymes I and II) content of the blood of pellagrins and of diabetics suffering from severe acidosis. Kohn,<sup>11</sup> using the same bacteriological method, has been unable to confirm the findings of the above authors relative to pellagrins. In partial confirmation of Kohn, Axelrod, and Elvehjem<sup>16</sup> have failed to observe a decrease in the Coenzyme I content of the blood of dogs manifesting an extreme degree of nicotinic acid deficiency.

Kohn and Klein,<sup>11,12</sup> using a bacteriologic assay method for Factor V, have shown that the concentration of this substance in human blood can be increased by the ingestion of large amounts of nicotinic acid. The "*in vitro*" synthesis of Factor V from nicotinic acid was also demonstrated. We have made a similar study using the more specific yeast fermentation method of von Euler<sup>5</sup> and Myrbäck<sup>15</sup> for the estimation of Coenzyme I. The results of this study form the basis for the present report.

**Experimental.** Blood was drawn by venepuncture and was placed in an oxalated flask. The analyses for Coenzyme I were carried out on the washed

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LEGEND FOR FIGURE 1.

FIG. 1.—EFFECT OF FEEDING 100 MG. OF NICOTINIC ACID PER DAY TO 5 NORMAL SUBJECTS AND 750 MG. PER DAY TO 1 PELLAGRIN UPON THE COENZYME I CONTENT OF BLOOD.

The first arrow designates the beginning and the second arrow the end of nicotinic acid administration. Blood Coenzyme I determinations were made at the points indicated.

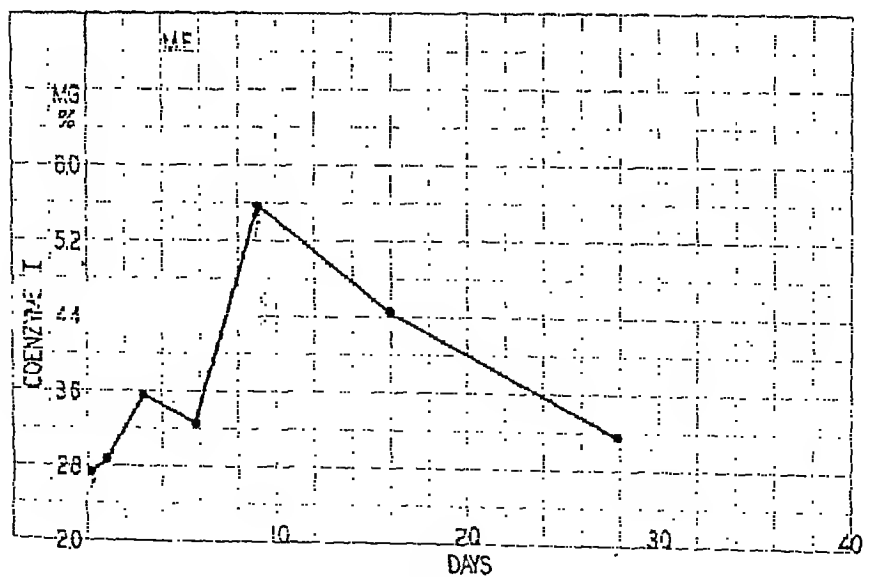
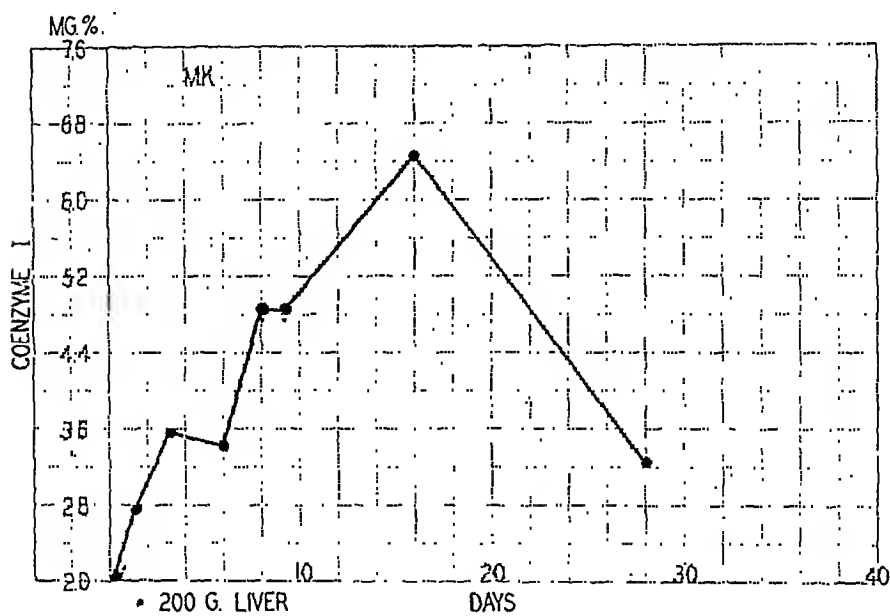
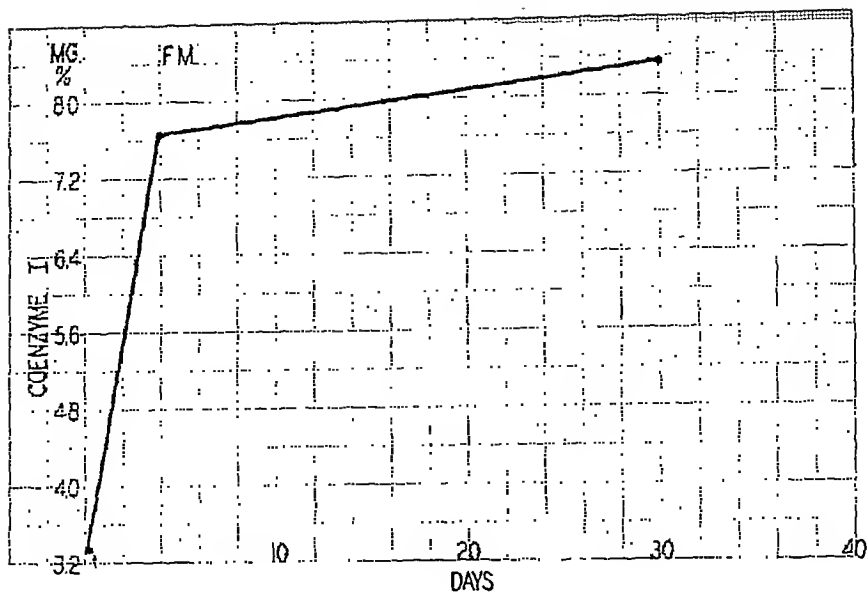
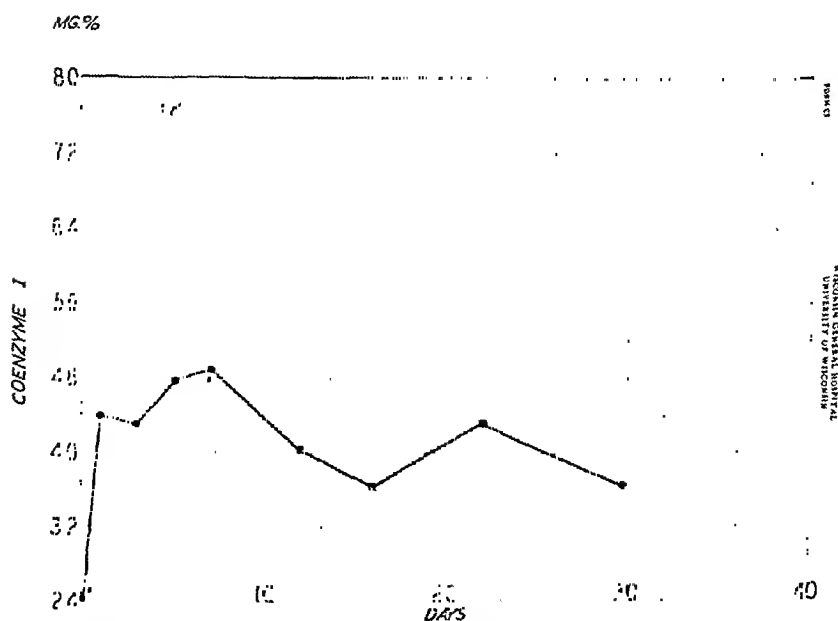
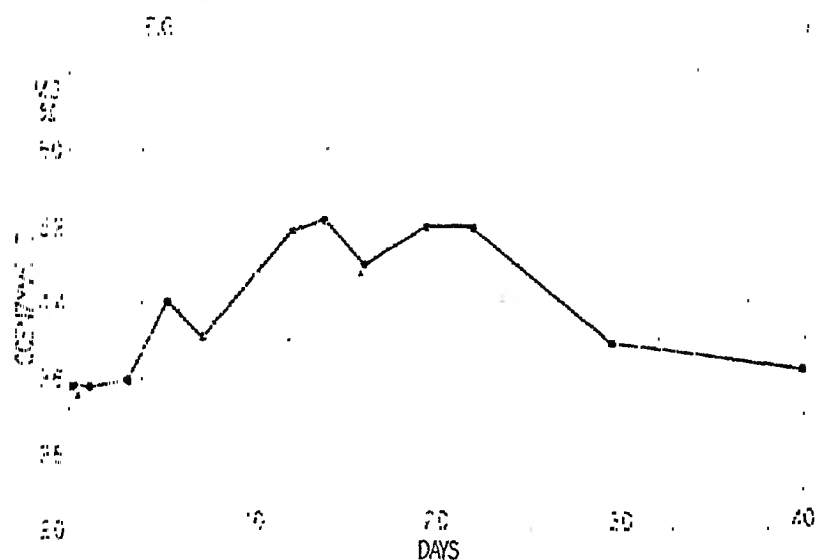
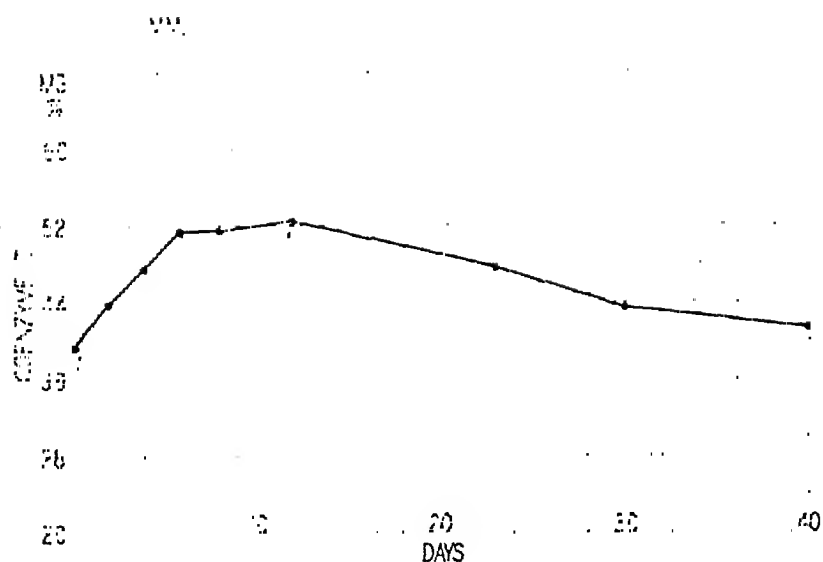


FIG. 1.



(700)

FIG. 1 (Continued)

red blood cells according to the technique described by Axelrod and Elvehjem.<sup>1a</sup> Hematocrit values were determined and the Coenzyme I content of the whole blood was calculated.

Five healthy subjects maintained on an otherwise normal diet received orally 100 mg. of nicotinic acid daily. Coenzyme I levels were determined for all of these individuals prior to the period of nicotinic acid administration. The dosage was continued for 1 to 2 weeks and the blood Coenzyme I levels were followed during this time. The results are indicated in the accompanying figures (Fig. 1).

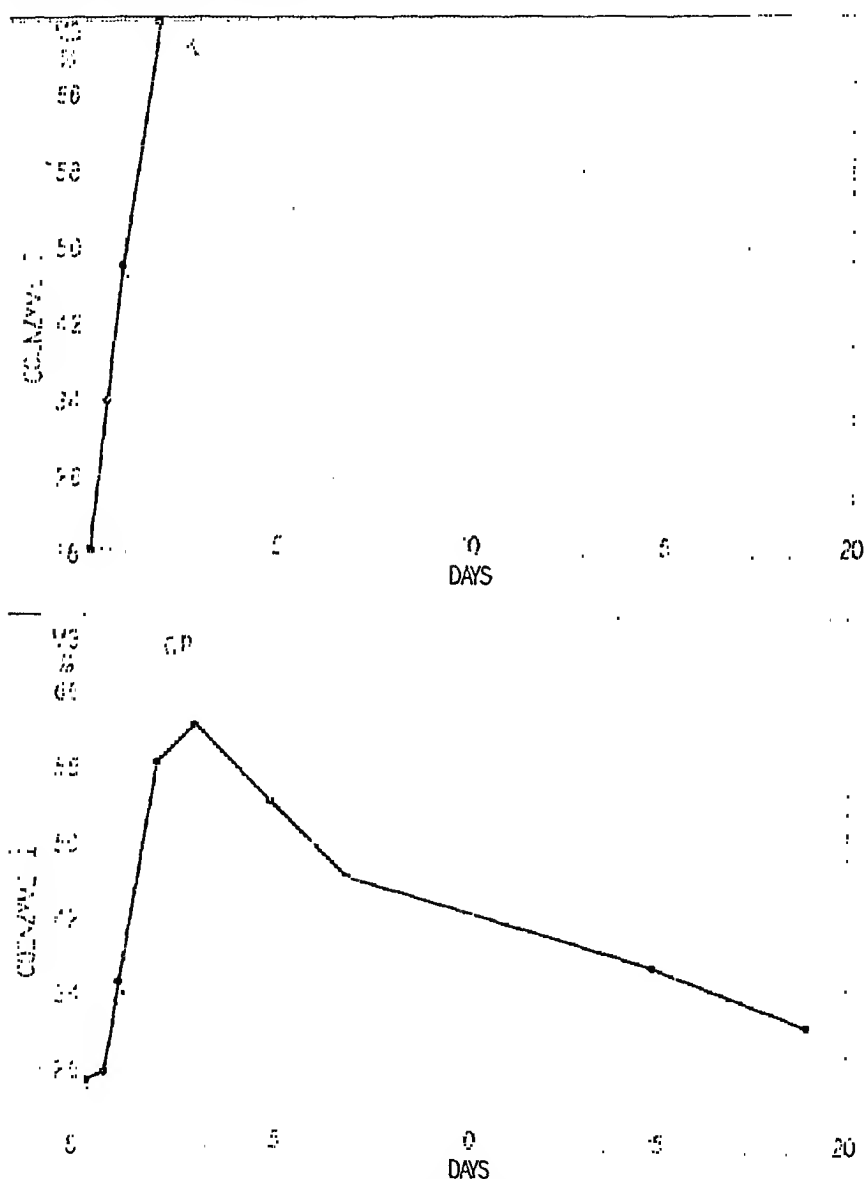


FIG. 2.—EFFECT OF FEEDING 1800 MG. OF NICOTINIC ACID WITHIN 16 HOURS UPON THE COENZYME I CONTENT OF BLOOD.

Arrows mark the beginning and end of nicotinic acid administration.

Two normal subjects were each given 1800 mg. of nicotinic acid over a period of 16 hours (200 mg. every 2 hours) and the response

in the Coenzyme I level of the blood noted. Blood samples were taken 8 and 25 hours after the administration of the initial dose of nicotinic acid (see Fig. 2). The striking vasodilating effect of nicotinic acid in both normal and pellagrous individuals was noted throughout these experiments. It was particularly troublesome when 1800 mg. of the vitamin were administered within 16 hours.

*Pellagrin (F. M.).* This patient, a 28-year-old unmarried colored woman, was admitted to the hospital complaining of attacks of dizziness. She had received violent trauma to the jaw 5 months previous to admission, resulting in a fracture with moderate deformity and failure of union. Because of this fracture and inability to use her jaws, she had subsisted wholly on liquids for 2 months and very little solid food during the entire 5-month period. More specifically, she consumed no vegetables, very little milk, almost no cereal and no meat during this entire time. Examination revealed marked emaciation. Her tongue and buccal mucous membranes were fiery red and very sore. Vincent's infection was evident over the gums. Skin over the hands, elbows, and feet was markedly thickened, cracked, and bleeding. There was definite muscular weakness with a suggestion of spasticity. Her mental state was very confused and she was almost maniacal at times. She was so belligerent upon admission that history and physical examination were difficult to obtain.

Laboratory studies showed a vitamin C level of 0.16 mg. per 100 cc. vitamin A of 1.42 "L" Units, prothrombin time of 100% and hemoglobin of 11 gm. per 100 cc. The blood Wassermann reaction was positive.

Coenzyme I studies were begun immediately after admission and were continued during the period of intensive therapy with nicotinic acid. The clinical response to this medication was immediate, with clearing of the mouth lesions and improvement of the mental state within 24 hours. Improvement in the skin lesions followed more slowly. An increase of 12 points in the patient's psychometric test was noted immediately after improvement in the mouth lesions had begun.

Results of the Coenzyme I studies are given in Table 3.

TABLE 1.—EFFECT OF THE ADMINISTRATION OF VARYING AMOUNTS OF NICOTINIC ACID UPON THE COENZYME I CONTENT OF BLOOD.

Subject.	Initial Coenzyme I, mg. per 100 cc.	Maximum Coenzyme I, mg. per 100 cc.	Per cent increase.	Period of administration.
E. G.* . . . . .	3.5	5.3	49	15 days
M. M.* . . . . .	3.9	5.1	31	10 "
A. K.* . . . . .	2.5	4.9	96	6 "
M. K.* . . . . .	1.9	4.9	150	7 "
M. E.* . . . . .	2.7	5.4	100	8 "
C. P.† . . . . .	2.5	6.3	152	16 hours
J. K.† . . . . .	1.8	7.4	310	16 "
F. M.‡ . . . . . (pellagrin)	3.4	8.3	144	30 days

\* Given 100 mg. per day.

† Given 1800 mg.

‡ Given 750 mg. per day.

**Discussion.** It is evident from the data presented that the Coenzyme I content of human blood can be increased by feeding

excessive amounts of nicotinic acid. These results are in complete agreement with those obtained by Kohn.<sup>11</sup> Supplementation of the normal diet with 100 mg. of nicotinic acid daily over a period of 10 days produces an average increase of 85% in the Coenzyme I content of the blood. The rate of this increase varies with the individual, as does the rate of return to normal after the period of administration of the vitamin has been completed. In general, the response to 100 mg. of nicotinic acid daily is not rapid and is followed by a slow drop to the normal Coenzyme I level after the nicotinic acid administration has ceased.

The rapid response following the ingestion of 200 gm. of fresh liver by one subject (M. K.) is very interesting. The degree of this response cannot be accounted for on the basis of the nicotinic acid content of the liver alone. The presence of other members of the vitamin B complex in the liver may be contributing factors (Vilter, Vilter, and Spies<sup>18b</sup>).

A very large and rapid rise in the Coenzyme I level of the blood follows the feeding of 1800 mg. of nicotinic acid over a period of 16 hours. In the two normal subjects studied, increases of 310 and 152% were observed within 48 hours after the administration of the vitamin. In the one case studied completely, a fairly rapid fall was noted soon after the maximum peak was reached.

The blood of pellagrin F. M. was normal in respect to its Coenzyme I content before nicotinic acid therapy was begun. This observation checks that of Kohn and indicates that Coenzyme I analyses of blood cannot be used as a diagnostic test for pellagra. An increase of 144% was obtained after the administration of 2 gm. of nicotinic acid over a 4-day period. This level was maintained for 1 month by the daily feeding of 750 mg. of nicotinic acid.

It is not reasonable to assume that the rapid rise in the Coenzyme I content of blood resulting from the administration of large amounts of nicotinic acid is caused by increases in the number of newly-formed cells containing abnormally large amounts of Coenzyme I. No change in hematocrit values was ever noted. We are inclined to the view that the nicotinic acid diffuses into the red blood cell from the plasma and is there utilized for the synthesis of the pyridine nucleotides. All of the Coenzyme I is confined to the corpuscles. Thus the rate of Coenzyme I synthesis would be a function of the nicotinic acid concentration of the plasma, the rate of diffusion of nicotinic acid into the red blood cell being the controlling factor. Such a mechanism would explain the results obtained when different levels of nicotinic acid were fed. A similar mechanism has been suggested by Kohn and Klein.<sup>12</sup> A complete answer to this problem must await the results of studies correlating the rate of formation of Coenzyme I in the red blood cell with the nicotinic acid concentration of the plasma. This type of study would also tend to clarify the present uncertainty regarding the explanation of the rapid fall

in Coenzyme I level after the feeding of large amounts of nicotinic acid has ceased. Is the normal rate of inactivation of Coenzyme I within the cell increased because of the presence of abnormally large amounts of that substance or does the increase in the rate of diffusion of Coenzyme I into the plasma account for the rapid fall in Coenzyme I level? The fact that neither of the pyridine nucleotides is ever detected in the plasma may be accounted for by the rapid inactivation of these substances by enzymes in the plasma. The usual course of cell destruction with the subsequent formation of red blood cells containing the normal amount of Coenzyme I does not seem to account for the rapid fall in Coenzyme I level. We find it difficult to accept the statement offered by Kohn<sup>11</sup> that "some fundamental difference exists between the initial V-factor found in the corpuscle and the increment which is rapidly added."

The fact that the Coenzyme I level of blood can be increased by the ingestion of large amounts of nicotinic acid leads to the belief that the coenzyme content of other tissues of the body may be influenced in the same manner. It has been demonstrated by Axelrod, Madden, and Elvehjem,<sup>2</sup> that this cannot be accomplished in the case of rat tissues, but the analogy should not be carried over into the case of the human species since present lines of evidence indicate that the rat can synthesize nicotinic acid while the human certainly cannot perform such a synthesis. The possible effects of an increase in the Coenzyme I level of body tissues with a corresponding increase in the general metabolic activity of these tissues becomes an interesting speculation.

The failure to observe a decrease in the Coenzyme I level of the blood of dogs suffering from nicotinic acid deficiency checks with the finding that the Coenzyme I level of blood does not decrease in human pellagra. However, other tissues of the dog (liver and muscle) do show a marked decrease in their Coenzyme I content, and it is entirely conceivable that the corresponding tissues of a pellagrin also possess a lowered coenzyme content.

**Summary.** 1. The Coenzyme I level of blood can be increased by the ingestion of large amounts of nicotinic acid.

2. The observed increases in the Coenzyme I level of blood vary with the amount of nicotinic acid fed.

3. The results of this study indicate that there is no diagnostic value to be obtained from determinations of Coenzyme I in borderline cases of deficiency disease.

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## INFLUENCE OF SEASON ON THE SEVERITY OF DIABETES AND ITS SCLEROTIC COMPLICATIONS.

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DIABETES as a disease seems definitely to be most prevalent and most severe among people living in middle temperate latitudes, and to become more benign and less frequent toward tropical warmth.<sup>5</sup> In middle temperate latitudes the disease also seems less troublesome during the lowered metabolic stress of summer warmth, but no statistics supporting this milder summer course have yet been published. In this brief note we wish to present an assay of the part season plays in diabetes severity at Cincinnati.

Feeling that frequency of hospital admission would provide a fairly valid index of disease severity, we surveyed the records of 1094 diabetic patients admitted to this hospital from May, 1923, to October, 1938, noting the month and year of hospital admission and any important complications that were present. Since circulatory stress and arteriosclerotic heart failure have been shown<sup>1</sup> to be unfavorably influenced by the winter season, we set aside for separate analysis the cases coming in because of sclerotic or vascular complications. Table 1 shows the distribution of admissions by year, sclerotic and non-sclerotic, as they occurred summer and winter. Case frequency within each year was too low for dividing the year into its four regular seasons, so we have restricted ourselves to a single division of each year. The winter division was taken to include the 7 months, October to April, or 58.15% of the year, the remaining 5 being classed as summer, 41.85% of the year. This uneven division was made because April in Cincinnati maintains the storminess and weather stress of winter, with little of the relaxing effects of summer warmth.

To investigate the effect of season upon admission frequency, we have compared the observed numbers of sclerotic and non-



sclerotic admissions in summer and winter with a normal distribution of case frequency, *i. e.*, 58.15% for winter and 41.85% for summer if season plays no part. In Table 1, we see that in 13 out of the 15 years the percentages of winter admissions because of sclerotic complications rise above the normal 58.15%, leaving only 2 of the 15 years in which the summer admissions because of sclerotic complications rise above the normal expectancy of 41.85%. With non-sclerotic admissions, on the other hand, the number of summer admissions exceed the expected 41.85% in 11 out of the 15 years, only 4 years showing winter admissions above the expected 58.15%. The non-sclerotic admissions deviated much less from their expected seasonal distributional percentages, however, than did those coming in for sclerotic complications.

TABLE 1.—ADMISSIONS OF DIABETIC PATIENTS FROM SCLEROTIC AND NON-SCLEROTIC CAUSES (MAY, 1923, TO SEPTEMBER, 1938).

Winter period.			Summer period.			Admissions as percentage of year's total.			
						Winter. Normal = 58.15		Summer. Normal = 41.85	
Oct. to April.	Sclerotic.	Non- sclerotic.	May to Sept.	Sclerotic.	Non- sclerotic.	Sclerotic.	Non- sclerotic.	Sclerotic.	Non- sclerotic.
1923-4	8	11	1923	3	8	73	58	27	42
1924-5	13	14	1924	5	20	72	41	28	59
1925-6	13	30	1925	13	17	50	63	50	37
1926-7	10	24	1926	3	26	77	48	23	52
1927-8	11	39	1927	4	11	73	78	27	22
1928-9	6	22	1928	5	17	56	56	44	44
1929-30	13	27	1929	4	36	76	43	24	57
1930-31	8	30	1930	3	19	73	61	27	39
1931-32	12	20	1931	7	15	63	57	37	43
1932-33	15	28	1932	4	10	79	74	21	26
1933-34	31	33	1933	4	40	89	45	11	55
1934-35	25	32	1934	8	31	76	51	24	49
1935-36	26	28	1935	3	28	90	50	10	50
1936-37	43	35	1936	8	42	84	45	16	55
1937-38	21	26	1937	3	43	87	38	13	62
	255	399		77	363	74.5	53.9	25.5	46.1

Handling the data mathematically, we find that the winter sclerotic admissions exceeded the expected 58.15% by  $15.33 \pm 2.05$ , with a corresponding deficit for the summer period. Winter non-sclerotic admissions fell  $3.67 \pm 1.90$  below the expected 58.15% of the total, while those of the summer showed the corresponding small rise above the expected 41.85%. The difference between the sclerotic and non-sclerotic groups in their seasonal admissions rates was  $19.00 \pm 2.80\%$ .

We see here a highly significant predominance of admissions for sclerotic complications in winter as compared to summer. The deviation of 15.33 from the expected 58.15% is 7.5 times its own probable error, meaning that such distribution would occur by chance only once in several millions of times. The non-sclerotic

winter admissions, on the other hand, deviated only 3.67 below the expected percentage (and those of the summer a similar amount above), this deviation being less than twice its own probable error and without significance.

Of the 1094 patients, 29 were admitted because of arteriosclerotic heart failure. It seemed justifiable to include these cases in our general calculation. Their removal produced slight change in the results, although 26 of the 29 were admitted in the "winter" period. With their exclusion, "winter" sclerotic admissions deviated  $16.00 \pm 2.11$  above the expected 58.15%, while the non-sclerotic fell  $4.00 \pm 1.94$  below. It should be borne in mind that by "sclerotic" and "non-sclerotic" admissions, we are referring to the type of complication causing the patient's entrance into the hospital. Many of the "non-sclerotic" admissions were of patients showing evidences of sclerosis, whose admissions into the hospital were not primarily because of the sclerotic complication but rather on account of the uncontrolled diabetic state.

In Table 2 are listed the sclerotic complications responsible for 332 of the total 1094 admissions, giving a rough idea of the part cardiovascular complications play in the diabetic picture at Cincinnati, with gangrene far outranking other sclerotic complications. Sclerotic complications were responsible for less than a third of the total diabetic admissions.

TABLE 2.—COMPLICATIONS CAUSING HOSPITAL ADMISSION OF DIABETICS (BY AGE GROUPS).

Age. 0-9	Gangrene.	Arterio- sclerotic and coronary heart disease.	Arterio- sclerotic heart failure.	Cerebral thrombosis or hemorrhage.	Chronic nephritis and/or uremia.	Cataract.	Total.
10-19	1						1
20-29						1	1
30-39	2	1	1	1		1	6
40-49	25	7	4	4	2	1	43
50-59	79	6	8	6	3	1	103
60-69	75	23	12	8	3	4	125
70+	33	8	4	5	1	2	53
Totals	215	45	29	24	9	10	332

From this statistical survey of hospital admissions, there would seem to be no evidence of seasonal effect on the severity of non-sclerotic diabetes at Cincinnati. This has been borne out also by a close check on the insulin needs of 20 well regulated diabetic patients observed for 2 years in the out-patient Diabetic Clinic. No difference could be found between summer and winter insulin needs, so long as the patients remained free of infectious fevers and adhered to their proper dietary regimen of fairly constant food intake the year round. Had a dietary increase been permitted during the more stimulating winter season, no doubt there would have been an accompanying increase in insulin need.

Others have reported increased winter hazards for the diabetic from his most troublesome vascular complication—gangrene. In Minneapolis, Beard<sup>2</sup> reported 95% of diabetic gangrenes as developing during the winter months. Blotner and Fitz,<sup>3</sup> in Boston, found 61% of gangrene cases to have an acute onset in the fall and winter months. Paulin<sup>6</sup> in his series of private patients at Atlanta, found no onset of diabetic gangrene from July to October, and a 79% occurrence from November to March. This high winter incidence of diabetic gangrene Joslin<sup>4</sup> attributes to lack of foot cleanliness during the cooler months, and he may be partially correct. But with all other vascular complications also showing increased severity in the cooler seasons, it would seem doubtful that lack of cleanliness would account for all the heightened winter gangrene hazards. Rather would one be inclined to attribute much of the winter trouble to increased spasm in a hyperactive vasomotor system and lessened blood flow through the extremities in the colder months.

**Conclusions.** The highly significant winter increase in admissions of diabetic patients whose diabetes is complicated by vascular troubles is due to the effect of the winter season upon the vascular complications and not to its effect upon the diabetic state. These findings verify the previously published data emphasizing the increased hazards of winter for arteriosclerotic and heart failure patients.<sup>1</sup>

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## THE EFFECTS OF CIGARETTE SMOKING AND DEEP BREATHING ON THE PERIPHERAL VASCULAR SYSTEM.

### STUDIED BY FIVE METHODS.\*

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NUMEROUS studies of the effects of cigarette smoking on the peripheral circulation agree that smoking induces vasoconstriction. Bruce, Miller, and Hooker<sup>4</sup> studied volumetrically the hands of 2

\* The expenses of this research were partially defrayed by the Philip Morris Fund.

patients and showed that smoking caused a fall in the volume of the hand. Similarly, Simici and Marcu<sup>22</sup> reported that in 3 habitual smokers there was an immediate fall in hand volume from smoking, while in 5 non-smokers, a rise preceded the fall in hand volume; in both groups the volume returned to normal within 15 minutes. The effect was negligible when the smoke was filtered through cotton soaked with ferric chloride solution. Lampson<sup>13</sup> studied 20 subjects, using a modification of the original Hewlett method,<sup>7,10</sup> and found that smoking resulted in a decrease in the blood inflow rate of from 57 to 83%. The fall lasted 60 minutes in those who inhaled the smoke and only 15 minutes in those who did not inhale.

Maddock and Coller<sup>16a</sup> reported that smoking caused a fall of 5.9° C. of the finger skin temperature. The smoking of cubebs, or the drawing of smoke through a water pipe or filtering it through ferric chloride virtually prevented the fall in skin temperature. Barker<sup>1</sup> reported a drop in cutaneous temperature of "1.8° C. or more," from excessive smoking (3 cigarettes in succession). Six of his 20 subjects showed no drop; 4 had a drop in finger temperature only; 5 in toe temperature only and 5 in both toes and fingers. Johnson and Short<sup>12</sup> reported that smoking caused an average drop of 4.3° F. in 88% of 26 habitual smokers and a drop of 3.2° F. in 3 of 8 non-smokers. Wright and Moffat<sup>25</sup> reported that all of their subjects who smoked a standard cigarette showed a drop in finger temperature averaging 5.3° F., while those who smoked denicotinized cigarettes had a fall of 4.8° F. They also concluded that "smoking without inhaling resulted in decreased effects on the surface temperature at the finger tips." Gamliel<sup>8</sup> in a study of cigarette smoking on 16 subjects failed to obtain any consistent effect on the skin temperature. Wright,<sup>24</sup> from observations of the capillaries at the finger nail-fold, described a slowing and often a stasis of the capillary circulation which was "appreciable only when the smoker inhales." He noted a "timal relationship to the deep inhalations" of the smoke, but concluded that "deep breathing of room atmosphere did not in any instance produce this result."

However, it has been shown that deep inhalations of air resulted in a shrinkage of the volume of the fingers,<sup>3,9</sup> and of the hand and forearm.<sup>23</sup> This loss in volume from a deep inhalation is due to arteriolar constriction in the hand and forearm.<sup>15,18,21</sup> Bolton, Carmichael and Sturup<sup>3</sup> showed that the vasoconstriction was reflex and depended upon intact vasomotor nerves. Because deep breathing is practised during the act of inhaling cigarette smoke and because the evidence offered in the literature on the vasomotor effects of smoking is inconclusive, the demonstration of arteriolar vasoconstriction in the hand from deep breathing has necessitated a reinvestigation of the subject. We have compared the effects of deep breathing and of smoking on the peripheral vascular system and have been able to demonstrate that the vasoconstriction as

shown by the fall in hand volume and the loss in skin temperature is largely due to the deep breathing performed during the act of smoking.

**Method.** The vascular status of the hand and lower forearm was determined by the use of 5 separate methods: 1, The pressure plethysmograph of Hewlett and Van Zwaluwenburg,<sup>10</sup> which measures the rate of blood inflow into the hand; 2, the simple plethysmograph which measures the changes in volume of the blood in the hand; 3, the skin calorimeter which is an indicator of the available heat of the skin; 4, the registering thermopile which measures the temperature of the skin; 5, microscopic observation of the capillary tufts at the nail-fold, which reveals the condition of the minute vessels and the behavior of the blood within them. Methods 1 and 2 measure the total flow through the lower forearm and hand and 3, 4 and 5 measure the blood flow through the skin of the fingers only. A more detailed description of the 5 methods has been made elsewhere.<sup>18</sup>

With Methods 1, 2 and 3 the subject must maintain the arm completely immobile lest movement mar the tracing. A dental chair insures comfort while the hand, usually the right, remains within the apparatus. For the simple plethysmograph experiments the subjects must remain especially quiet, therefore during the smoking, the cigarette was held by the observer and was brought to the lips of the subject every 30 seconds, for from 9 to 12 puffs. The subject was allowed to rest for at least  $\frac{1}{2}$  hour before any procedure was begun in order to insure a basal state of blood flow. The room temperature was usually about 25° C. and the relative humidity between 50 and 60. All subjects were studied thoroughly before, during, and after smoking. Each observation period consumed from 1 to 2 hours, the 5 methods requiring at least 4 sessions for each subject. Only one cigarette was smoked during an experimental period except when otherwise noted. Although the subjects were requested to refrain from smoking for at least 1 hour before coming to the laboratory, none of them were asked to smoke sooner than 1½ hours after the experiment was begun. The effects from smoking standard cigarettes were also compared with the effects from denicotinized cigarettes. The latter were either plain or filtered through a cigarette by means of a Zeus holder, in which manner much of the nicotine<sup>11</sup> and tar<sup>17</sup> were removed from the cigarette smoke as it filtered through the unburnt tobacco. Occasionally, both a standard brand cigarette and a denicotinized cigarette were smoked during one experimental period.

The responsiveness of the peripheral vascular system of each subject was tested prior to any smoking by a series of 10 deep breaths, often by a single deep breath, and by a painful pinch of the skin of the forearm. The vasomotor responses of the hand to the deep breathing were compared with the effects of smoking, any qualitative differences being attributable specifically to the smoke. Each of the 10 deep breaths was taken at 15-second intervals. The average number of inhalations of smoke taken by the "inhale" groups was 11.2 (7 to 22) in 7.7 minutes, and the average number of puffs taken by the "non-inhale" group was 21 (16 to 25) in 7.8 minutes. As a rule, the hand volume, measured with the plethysmograph, and the skin calorimeter determinations were made simultaneously throughout the smoking period and for 15 minutes after the subject stopped smoking. The 21 subjects used in this study were medical and dental students of the second year class. There were 17 habitual smokers who inhaled and who had been smoking about a package of cigarettes a day for an average of 6.4 years.

**Results. HEWLETT METHOD.** The hand is placed in a plethysmograph which is recording upon a kymograph. A 70 mm. Hg

pressure is applied suddenly to the forearm by means of a 5 cm. cuff placed just above the diaphragm of the plethysmograph and the increment in hand volume is recorded. Each increment tracing consists of 2 or more parts, namely: the initial ascent, which indicates the rate of blood inflow and is computed in cubic centimeters per minute per 100 cc. of hand volume; and a secondary less steep slope, which gradually approaches the horizontal within 1 minute of the application of the pressure. The height thus attained is designated as "capacity volume," and depends upon the tonus of the blood-vessels, the number of patent minute vessels, and upon the arteriolar pressure just prior to the application of the obstructing pressure. The method is discontinuous, and a minimum of 2 minutes is allowed to elapse between readings. Tables 1 and 2 show the results obtained by the Hewlett method on the rate of blood inflow and on the "capacity volume" from smoking and from deep breathing.

TABLE 1.—BLOOD INFLOW RATES OBTAINED WITH THE HEWLETT METHOD.

[No. of subjects.	Inflow rates cc. per min. per 100 cc. hand vol.		Per cent change.	Procedure.	
	Before.	After.			
17	9.1	..	..	Basal after $\frac{1}{2}$ hour rest.	
10	8.9	4.6	-48	After 10 deep breaths taken in 2.5 minutes	9 of these subjects are in both groups.
11	9.6	6.4	-33	During smoking (inhaling) for 7.7 minutes	
7	9.4	13.2	+40	After 10 deep breaths taken in 2.5 minutes	5 of these subjects are in both groups.
6	8.1	11.9	+47	During smoking (inhaling) for 7.7 minutes	

*"Inhale" Group.* The average rate of blood inflow in 17 subjects at rest was found to be 9.1 cc. per 100 cc. of hand volume per minute. The blood inflow rate in 10 of the 17 subjects dropped on an average of 4.3 cc. (48%) immediately following 10 deep breaths. During the smoking of a cigarette the average inflow rate fell 3.2 cc. (33%) in 11 of the 17 subjects. Nine of the 10 subjects who showed a fall in rate of inflow from deep breathing also showed a fall from cigarette smoking. The similarity of response from the 2 procedures in many of the subjects suggests that the vasomotor reaction to the smoking of a cigarette is due in part to the accompanying deep inhalations.

The capacity volume in 16 subjects at rest averaged 11.3 cc. After 10 deep breaths, 10 subjects showed a rise from a resting volume of 10.6 cc. to an average of 16.6 cc., an increase of 6.0 cc. (57%). During cigarette smoking, the volume rose in 11 of the 16 subjects from a resting level of 10.2 cc. to an average of 14.2 cc., an increase of 39%. Six of these continued high for at least 10 minutes upon cessation of smoking while the others fell to normal.

TABLE 2.—CAPACITY VOLUME OF THE HAND.  
(One Minute After 70 mm. Hg Pressure to Forearm.)

No. of subjects.	Capacity, vol. in cc.		Per cent change.	Procedure	
	Before.	After.			
16	11.3	..	..	Basal after $\frac{1}{2}$ hour rest.	
10	10.6	16.6	+57	After 10 deep breaths taken in 2.5 minutes	9 of these subjects are in both groups.
11	10.2	14.2	+39	During smoking (inhaling) for 7.7 minutes	
3	14.3	11.7	-18	After 10 deep breaths taken in 2.5 minutes	2 of these subjects are in both groups.
2	15.7	11.3	-28	During smoking (inhaling) for 7.7 minutes	
2	10	10.3	..	After 10 deep breaths taken in 2.5 minutes	1 of these subjects is in both groups.
3	14	13.8	..	During smoking (inhaling) for 7.7 minutes	

Nine of the 16 subjects showed a rise in volume both after the 10 deep breaths and after smoking. The arteriolar vasoconstriction from deep breathing results in a partial emptying of the more peripheral minute vessels. These are stretched and refilled again when the collecting pressure is applied. Therefore, when, after a deep breath, the venous outflow is obstructed with a 70 mm. Hg pressure there is added to the resting level "capacity" blood volume of the hand that amount of blood which has been lost. This rise in capacity volume is therefore not a true increase in the amount of blood held in the hand but is actually a measure of the amount of blood which had escaped due to the vasoconstriction. These losses were 6.1 cc. from 10 deep breaths and 4.0 cc. from cigarette smoking, and compare well with the volume reductions obtained with the simple plethysmograph (see p. 713). Figure 1 illustrates the usual effect on the blood inflow rate and capacity volume of the hand from 10 deep breaths and from cigarette smoking.

*"Non-inhale" Group.* In 4 subjects the average resting blood inflow rate was 8.9 cc. Following 10 deep breaths all 4 decreased in rate an average of 4.9 cc. Simple puffing of smoke caused an average decrease in rate of 3.7 cc. in 3 of the subjects, and no change in 1 subject.

In 2 of the subjects 10 deep breaths caused a rise in "capacity volume" of 2.5 cc. and 2.0 cc.; and in 2 there was a fall of 4.5 cc. and 0.5 cc. Puffing of cigarette smoke decreased the "capacity volume" by 0.3, 0.7, and 4.2 cc., and increased it in the fourth subject by 2.6 cc.

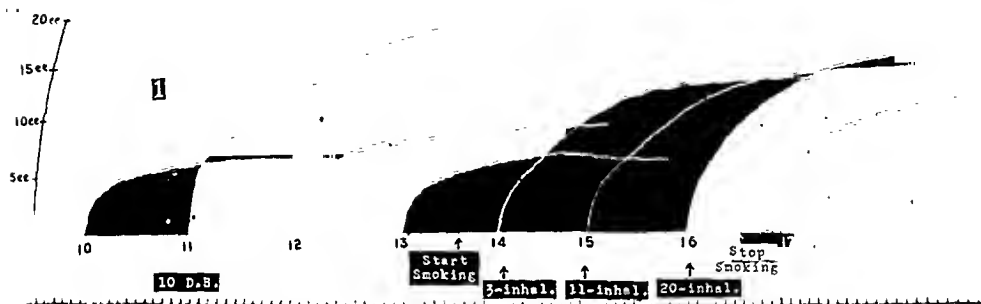


FIG. 1.—Records of blood inflow rate of right hand made with the Hewlett method showing the similar effects obtained from 10 deep breaths and from smoking a standard brand cigarette. Curves 10 and 13 are normal and represent an inflow rate of 10.6 cc. per min. per 100 cc. of hand volume and a "capacity hand volume" of 7 cc. Curve 11 represents an inflow rate of 18.3 cc. and a "capacity hand volume" of 19.5 cc. Curves 14, 15, and 16 represent an average inflow rate of 13.8 cc. and an average "capacity hand volume" of 15.3 cc. Smoking time is 7 minutes. Time is in seconds.

**THE SIMPLE PLETHYSMOGRAPH.** This method, in which the pressure cuff is not used, has the advantage of being continuous. It has been used to measure changes in the volume of the hand resulting from deep breathing or from smoking. The results are given in cubic centimeters of volume change and are not corrected for unit volume of the hand. Only differences greater than 0.5 cc. are considered as significant. The figures yielded by the simple plethysmograph are of themselves difficult to interpret. The fall in volume of the hand which occurs from deep breaths of air or of smoke represents a loss of blood from the part within the plethysmograph. This loss may be due to a decrease in the inflow rate, to a fall in arteriolar pressure, or to a constriction or obliteration of some of the minute vessels. The experiments were performed upon 17 subjects, of whom 15 inhaled; and 2 merely puff-smoked the cigarette.

*"Inhale" Group.* Nine of the 15 subjects who inhaled smoke from a standard cigarette showed a greater loss in hand volume (10.8 cc.) than from 10 deep breaths (6.8 cc.). Four subjects gave a loss in hand volume of 7.6 cc. from 10 deep breaths as compared to a loss of 5.1 cc. from the smoking of a cigarette; 1 showed the



same loss from both procedures and 1 showed a rise in volume of 1.5 cc. from smoking and a fall of 6.5 cc. from deep breathing. However, repeated observations upon these subjects disclosed large variations in response from day to day and occasionally a reversal of the smoking:10-deep-breath relationship.

Ten subjects smoked commercial denicotinized cigarettes and the effects were compared with those from the smoking of standard cigarettes or from 10 deep breaths. In 9 of these, the smoke from the denicotinized cigarette was filtered in order to lower further the nicotine content of the smoke. The smoking of denicotinized cigarettes caused a loss of hand volume averaging 11.7 cc., larger by 0.9 cc. than the average loss from the smoking of standard cigarettes. Three subjects who showed a small fall in hand volume from the smoking of the denicotinized cigarette showed immediately upon recovery a similar small fall from a standard cigarette. The similarity of response to the two types of cigarettes suggests that the nicotine content of the smoke plays a minor part in the causation of the fall in hand volume.

*"Non-inhale" Group.* There were 2 subjects, one of whom showed a loss of 7 cc. from both 10 deep breaths and from cigarette smoking; the other showed a loss in hand volume from deep breathing 12 cc. greater than from smoking.

*SKIN CALORIMETER.* The available heat at the finger-tip was measured by the apparatus of Mulinos and Shulman.<sup>18</sup> The E. M. F. from a "conducting" thermocouple was recorded by a sensitive galvanometer which was calibrated to give a deviation of 5 cm. per degree temperature change between the variable and "cold" junctions. Only changes greater than 0.5 cm. were considered as being significant. This apparatus has the advantage that it responds more quickly than the usual skin thermometer thermocouple to small changes in blood flow in the skin. By this means we were enabled to detect a change in skin blood flow from a single deep breath.<sup>18</sup>

*"Inhale" Group.* Eleven of the 16 subjects showed a greater fall of available heat from the finger due to smoking a standard cigarette than from 10 deep breaths. Two subjects showed a similar fall from the two procedures while 3 showed a greater fall from 10 deep breaths. One of these subjects who had previously shown a rise in hand volume from smoking now had an increase in the available heat; whereas deep breathing always resulted in a fall. Eight subjects who smoked commercial denicotinized cigarettes showed a fall in available heat. In 4 the fall was equal to or greater than that from a standard cigarette. The effects of smoking a standard cigarette were determined a second time on 5 subjects. Four showed a smaller fall in available heat and one a greater fall when compared with the previous smoking and demonstrates the variability of the reaction.

*"Non-inhale" Group.* Three of 4 subjects had a greater fall in

available heat from 10 deep breaths than from puffing cigarette smoke. The fall due to puffing a standard brand cigarette was less than from deep breathing or from the inhaling of smoke.

**SKIN TEMPERATURES.** The skin of a finger provides the most sensitive temperature gauge of the circulation to the skin of the limb as a whole.<sup>14</sup> The skin temperature was determined by means of a thermopile composed of 48 thermo-junctions of silver constantan.<sup>18</sup> The electromotive force developed by the thermopile was recorded on a Micromax millivolt meter calibrated to read in degrees.

The skin temperature is always above that of the room except when the circulation is arrested and evaporation is occurring. In our apparatus the thermo-junctions are covered completely by the skin of the finger, so that any sweat which may occur does not evaporate so readily, nor are currents of air so likely to affect the temperature of the junctions as is the case with some of the single couples available for this type of work. It has been shown that the fall in skin temperature due to complete obstruction of blood flow is proportional to the difference between the room temperature and the skin temperature.<sup>18</sup> Complete obstruction of all blood flow in the forearm for 5 minutes resulted in a fall in skin temperature of about 32% of the skin temperature-room temperature difference. Lewis obtained a fall of 7° C. from an obstruction of 34 minutes or a 64% differential. From these figures it is obvious that drops in skin temperature of as high as 15.5° F. (9.7° C.) which represent differentials from 80 to 100+ % reported by Wright and Moffat to result from smoking must have been due to factors not operative in our own technique. The maximum fall in skin temperature observed by us was 2.8° C., a figure which agrees well with those reported by Barker<sup>1</sup> and by Lampson.<sup>13</sup>

Thirteen of the 19 subjects studied showed a greater average drop (0.79° C.) from cigarette smoking than from deep breathing (Fig. 2). In the "inhale" group the drop in skin temperature varied from 0.35° C. to 2.18° C. and in the "non-inhale" group from 0.24° C. to 0.51° C. The slight fall in skin temperature from puffing corroborates both the results obtained by the other procedures and those reported in the literature.

Five subjects showed a smaller fall (0.53° C.) in skin temperature from inhaling than from 10 deep breaths (Fig. 3), and one subject had the same fall from both procedures. The fall in skin temperature from 10 deep breaths varied from 0.35° C. to 2.27° C., figures which are not very much different from those obtained from inhaling of smoke.

The skin temperature in 10 of the 19 subjects returned to normal in from 2 to 10 minutes after cessation of smoking; 5 subjects were one-half to three-fourths recovered within 7 minutes, the experiment having been terminated due to restlessness; 2 subjects returned to their normal skin temperature during the smoking of the cigarette

while 1 subject showed no recovery after 45 minutes. The fall in skin temperature from 10 deep breaths was recovered from on an average of 4.1 minutes (2 to 9).

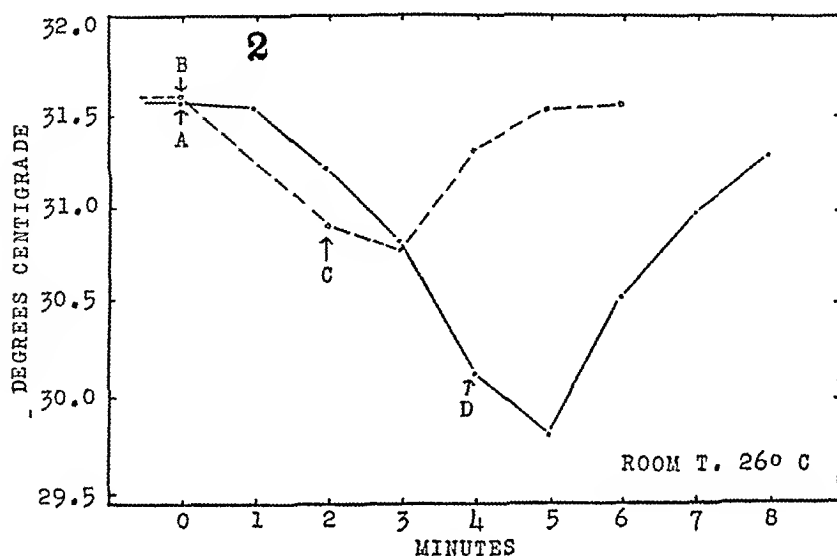


FIG. 2.—The effect of 10 deep breaths and of smoking upon the finger skin temperature. This is a graph representative of 13 subjects who reacted more to smoking than to deep breathing. Dotted line: 10 deep breaths taken between *B* and *C*. Solid line: smoking a standard brand cigarette from *A* to *D*.

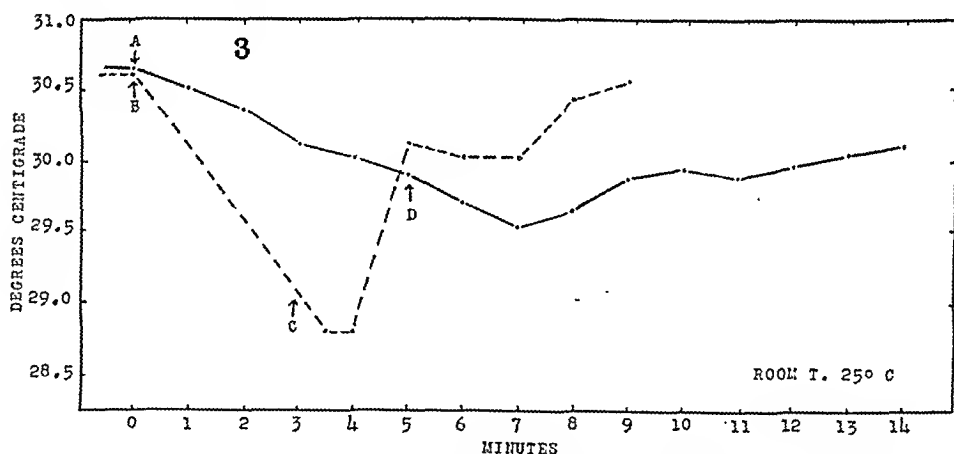


FIG. 3.—A graph of finger skin temperature as in Figure 2. This is representative of 5 subjects who reacted more to deep breathing than to smoking.

**CAPILLARY OBSERVATIONS.** These were made at the nail-fold of the finger using the Leitz Ultropak microscope objective. With this instrument it is possible to note the length, width, and tortuosity of the capillary tufts; their number and the approximate rate of blood flow through them. Small changes in the rate of flow through the capillary tuft are difficult to observe, while long observation periods

reveal obvious changes in blood flow rates which are apparently "spontaneous." Deep breathing, sighing, coughing, or talking result in such changes, and make interpretation difficult. In 80% of 45 subjects a deep breath was followed by a complete cessation of the blood flow in the tufts, lasting from 3 to 5 seconds. Blood flow within the tufts appeared to have returned to the normal rate within 5 to 15 seconds after the deep breath.<sup>18</sup>

*"Inhale" Group.* Of 16 subjects observed, 11 showed a timal relationship between the inhaling of the cigarette smoke and the slowing or stopping of the flow through the capillaries; 3 showed a slowing independent of the inhalations and in 2 there was no effect. In 13 of these subjects a single deep breath was followed by complete cessation of blood flow through the capillary tuft, and in 3 there was slowing but no stoppage. Wright<sup>24</sup> likewise noted that the slowing of the capillary flow seemed appreciable only when the smoker inhaled. However, he stated that deep breathing of room air alone did not in any instance produce this result.

*"Non-inhale" Group.* None of the 4 subjects who puffed cigarette smoke showed a cessation in capillary blood flow although there was some slight slowing. A deep breath resulted in complete cessation of blood flow in 3 of the 4 subjects.

**Discussion.** Cigarette smoking is usually accompanied by deep inhalations of the smoke which is taken into the mouth, so that the inhaler absorbs more of the nicotine and other products of tobacco combustion and exposes a greater mucous surface to the irritant properties of the smoke than would be the case if inhalation were not practised. The vasoconstrictor response to a pinch<sup>5</sup> or other painful stimuli, and to the inhalation of ammonia,<sup>18</sup> suggests that irritation may play a part in the production of peripheral vasoconstriction. However, vasoconstriction has been shown to result from the deep inhalation of air alone.<sup>3,15</sup> The act of inhaling cigarette smoke, therefore, is associated with three factors each of which may independently produce peripheral vasoconstriction. These are: 1, the pharmacologic activity of the constituents of the smoke (nicotine, etc.); 2, irritation; and 3, the deep inhalation. The combination of all three factors results in a greater effect than does any one alone.

In the present study, we attempt to determine the importance of each of these factors in the production of the vasoconstriction from smoking. With the five methods described, it has been possible to prove that the inhalation of smoke results in constriction of the arterioles of the forearm and hand indistinguishable from the constriction which follows deep breathing. Maddock and Coller,<sup>16b</sup> Wright,<sup>24</sup> and Lampson<sup>13</sup> had already made the observation herein confirmed that only smokers who inhaled showed any considerable fall in skin temperature or reduction in the blood inflow rate.

Numerous facts militate against the assumption that much of the

vasoconstriction from the inhalation of cigarette smoke is due to nicotine, despite the fact that Maddock and Collier<sup>16b</sup> found that "nicotine administered intravenously in quantities not greater than that theoretically absorbed in the smoking of 1 or 2 cigarettes produced comparatively analogous changes." Baumberger<sup>2</sup> has shown that the smoker retains 88.2% of the smoke which he inhales and 66.7% when puffing alone is practised. In our experiments, the subjects who inhaled the smoke took but 11 inhalations as against 21 puffs for the "non-inhalers." It is possible that the total amount of nicotine retained by the "non-inhale" group is greater than in the group that inhaled, yet the subjects who inhaled the smoke showed the greater and more persistent vasoconstriction. It may be that of the nicotine which was abstracted by the mucous membranes, more was absorbed from the lungs than from the mouth. Furthermore, we were able to confirm Wright and Moffat<sup>25</sup> and Johnson and Short<sup>12</sup> in their observations that heavy smokers show well developed vasoconstriction, despite the fact that systemic reactions are less likely to occur in such subjects than in occasional smokers. Wright and Moffat<sup>25</sup> stated that "there was no appreciable effect on the forehead temperature during any of these experiments," and Maddock and Collier<sup>16b</sup> had failed to obtain vasoconstriction of the skin at the waist. This selective action of nicotine is pharmacologically unlikely.

Further confirmation of the secondary importance of nicotine is to be found in the facts adduced in the present report (a) that the smoke from "denicotinized" cigarettes was as effective in eliciting vasoconstriction as was the smoke from standard cigarettes; (b) that the inhalation of air alone caused vasoconstriction nearly equal to that following the inhalation of smoke; and (c) that 3 subjects who smoked a standard cigarette unusually rapidly became dizzy, pale and weak, with beads of perspiration appearing on the forehead. All developed nausea and one vomited, yet neither by the Hewlett nor by the plethysmograph methods could there be demonstrated any vasoconstriction in the hand that could be ascribed to the smoking. The experiments performed on these subjects were not included in the above report because we felt that the smoker voluntarily stopped short of being sick and we wished to limit our observations to "physiological" smoking. Segal<sup>20</sup> has found that the smoking of standard or of denicotinized cigarettes produced identical changes on the electrocardiogram: an increase in heart rate, and a lowering of the *T*-wave. Carlson<sup>6</sup> found that the promptness with which the gastric hunger contractions were inhibited by smoking 1 cigarette indicated a reflex rather than a nicotine inhibition. Schnedorf and Ivy<sup>19</sup> found that smoking stimulated the flow of saliva reflexly, for the flow of saliva was not increased by the nicotine absorbed from 2 or 3 cigarettes. In 20 ulcer patients the differences between the decrease in acidity ob-

tained with denicotinized and with ordinary cigarettes were not statistically significant.

The degree of vascular reaction to smoking varies markedly in different individuals and in the same subject from day to day. This variation occurs also to deep breathing;<sup>18</sup> to a pinch<sup>5</sup> or to smelling salts. Baumberger<sup>2</sup> has shown that the weight of the smoke taken into the mouth varied from 0.1 to 6.9 mg. per puff, and Jensen and Haley,<sup>11</sup> determining nicotine chemically, concluded that the composition of the smoke varied inversely as the moisture of the cigarettes; directly to the strength of the puff and to the length of cigarette already smoked.<sup>17</sup> In view of so many factors which may contribute to the variability of the vascular reaction to smoking, it is necessary to perform numerous comparative experiments upon a number of well controlled individuals, the reactions of whom thus become established by experiment. During any single experimental period the subject should be tested with such procedures as deep breathing, pinching, and so on, before and after the crucial procedure. Only in this way can one evaluate the extraneous factors enumerated above.

**Summary.** Using 5 different methods, an analysis of the response of the peripheral vascular system to smoking and deep breathing has led to the following conclusions:

1. Deep breathing alone can account for the greater part of the decreased blood inflow rate, the loss of hand volume and the drop in skin temperature of the hand resulting from the inhalation of cigarette smoke.

2. The subjects who did not inhale cigarette smoke showed a greater vascular response of the hand from 10 deep breaths than from the puffing, and a lesser response than those who inhaled the cigarette smoke.

3. Inhaling the smoke from denicotinized cigarettes resulted in as great and occasionally greater vasoconstriction than the inhaling of the smoke from a standard brand cigarette.

4. The degree of response of the peripheral vascular system varies markedly among individuals and in the same subject from day to day.

5. The vasoconstriction due to smoking lasts about 15 minutes (7 to 45). These figures are at variance with the conclusion that "If . . . a patient should smoke 1 cigarette an hour he would depress his peripheral circulation during the entire day."<sup>13</sup>

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## BOOK REVIEWS AND NOTICES

**NEW FACTS ON MENTAL DISORDERS.** Study of 89,190 Cases. By NEIL A. DAYTON, M.D., M.C., Director, Division of Statistics, and Director, Division of Mental Deficiency, Massachusetts State Department of Mental Health, etc. Pp. 486; 110 graphs; 84 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, \$4.50.

CONTENDING that previous studies of mental problems have been largely analysis of the individual with a mental disorder, the author here visualizes the approximate 90,000 admissions to Massachusetts mental hospitals, from 1919-1933, inclusive, "as one large individual," thus giving a study in averages. Some of the analyses and conclusions follow: Old age, not in middle life, now reveals the maximum incidence in mental disorder. It appears men are breaking down faster than women. Our national mode of living is not conducive to health or longevity after 40 or 50 years. Highest admission rates are presented by our foreign born; being accustomed to hardships, however, they endure unemployment and depression better than our more prosperous natives. Taking all admissions, alcohol is the outstanding factor in the mental history. "The first year of Prohibition, 1920, shows both the low for alcoholism and the lowest admission rate of the entire period, 1919-1933." That the psychotic individual took to alcohol when in financial difficulty, as an "escape from reality," is not substantiated by this study. The married are less likely to develop mental disorders than others, in the following order—widowed, single and divorced. The single man shows 60% more mental disorders than the single woman. After disunion, man shows about 40% more than woman. Hebrews, either single or married, present the highest percentage of patients. The great immigrant inflow, has added enormously to our many social, economic and public health problems. The assembling of all these data has been a prodigious task, to which no short review can do justice. Doubtless the book will be widely read and will supply the lead for much additional research. The bibliography is scant but the index is adequate.

N. Y.

**MEDICAL CARE (A Symposium).** Law and Contemporary Problems. Volume VI, No. 4, Autumn, 1939. (A Quarterly Published by the Duke University School of Law, PROF. DAVID F. CAVERS, Editor.) Pp. 185. Durham, N. C.: Duke University School of Law, 1939. Price, 75c.

THIS number of the Duke University quarterly dealing with Law and Contemporary Problems, is devoted to medical care. The subject is introduced by an excellent paper on the national problems in medical care by J. S. Falk, who, after sketching the history of the problem, discusses the social objectives in a health program, needs to be met, and the existing basis for a health program in this country. There follow 8 papers dealing with various experiments that are being tried as means of furnishing adequate medical care to groups of the population. The last 5 papers consider the problems related to federal legislation as embodied in the Wagner Bill. This symposium discusses especially the legal aspects of plans for medical care, and should prove of interest and value to those concerned with problems related to health legislation.

G. R.



**SCLEROSING THERAPY.** The Injection Treatment of Hernia, Hydrocele, Varicose Veins and Hemorrhoids. Edited by FRANK C. YEOMANS, M.D., F.A.C.S., M.R.S.M. (LOND., HON.), Professor of Proctology and Attending Surgeon, New York Polyclinic Medical School and Hospital, etc. Pp. 336; 117 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.00.

THE rise of the use of sclerosing solutions in the treatment of various types of surgical diseases has made a place for this volume. It concerns especially the use of sclerosing solutions in the treatment of hernia, hydrocele, varicose veins and hemorrhoids. Each section is written by a man who speaks with some authority due to a wide clinical experience. The first section is on the injection treatment of hernia by Dr. Bratrud, who points out that the success of this measure depends upon a thorough understanding of the anatomy of the inguinal region. The section is well illustrated by drawings and photographs. An excellent chapter on trusses emphasizes that the success or failure of the treatment depends on the satisfactory fitting of the truss. In the chapter on the technique, he describes and illustrates his method of injection and enumerates the various solutions which he uses. He injects not only direct and indirect inguinal hernias but also femoral and umbilical hernias. He found a recurrence of 9% in indirect inguinal hernias, 18% in bilateral indirect hernias and 17% in direct inguinal hernias. Recurrence was very low in the younger age group, and greatest in patients between 50 and 60 years of age. However, many cases which had been accepted for injection treatment had very definite contraindications for surgery. He recommends the injection treatment for recurrences of hernia following operation. Part II, on the injection treatment of hydrocele and written by Dr. Hoch, is relatively short and well illustrated by McNett. Hoch aspirates the fluid from the hydrocele and injects a solution of quinine hydrochloride 13.33% with urethane 6.66%, usually injecting 2 to 4 cc. If recurrences appear, aspiration and injection may be repeated. Part III, on the injection treatment of varicose veins (by Dr. Shelley), takes up the history of this procedure, the anatomy of the veins of the legs, the causes of varicose veins, symptomatology, diagnosis and the various tests used. The techniques of injection and of ligation of the veins are those which are commonly employed. The author gives a very good chapter on the treatment of complications and insists upon the patient being ambulatory after injection if possible. Part IV, a discussion of the injection treatment of hemorrhoids (Dr. Yeomans) is written largely from the experience of the author. He states that his results in a large number of cases has been very satisfactory, with no deaths or serious complications. The book is one for use by young men who are willing and anxious to learn this relatively new type of treatment of various surgical lesions. It is well printed and well illustrated and is a definite contribution to its field.

L. F.

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**BIOLOGICAL PRODUCTS.** By LOUIS GERSHENFELD, P.D., B.Sc., Ph.M., Professor of Bacteriology and Hygiene, and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science, etc. Pp. 242; illustrated. New York: Romaine Pierson Publishers, Inc., 1939. Price, \$4.00.

THE details of manufacture are given for the various products included under the term "biological products," such as the antitoxic sera, antibacterial sera, vaccines, toxoids and the numerous products employed for diagnosis and treatment in the various allergic conditions. Such a compilation of information should be of help to teachers and research workers. Vitamin products and glandular products are not included. H. M.

BEYOND THE CLINICAL FRONTIERS. By EDWARD A. STRECKER, A.M., Sc.D., Litt.D., M.D., Professor of Psychiatry in the Undergraduate and Graduate Schools of Medicine, University of Pennsylvania, and Consultant and Chief-of-Service, Institute of the Pennsylvania Hospital. Pp. 210. New York: W. W. Norton & Co., Inc., 1940. Price, \$2.00.

In this volume, one of the Salmon Memorial Lectures, the writer endeavors to show a relationship between the mentally ill, the normally thinking individuals and crowd mass behavior. Some of the subjects discussed follow: The retreat from reality in the psychoses and psychoneuroses each individual's life in a private world of his own making; a few of the natural, artificial and pathologic aids for softening hard realities; the everyday prototypes of symptoms of mental disease; the "mores" of mental patients which may not be altogether without profit to civilized culture; the serious predicaments of our civilization, the great need for mental hygiene; and the stimulating analogy of physical hygiene. Suggestions toward combatting some of our cultural evils. This thesis shows a compromise between a popular and a technical rendering. The bibliography includes current fiction. N. Y.

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THE INTER-RELATIONSHIP OF MIND AND BODY. (The Proceedings of the Association; New York, December 27 and 28, 1938). Editorial Board: FOSTER KENNEDY, ANGUS M. FRANTZ AND CLARENCE C. HARE. Pp. 381; 28 illustrations and 10 tables. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.00.

Of the 22 collaborators, most are members of the Association for Research in Nervous and Mental Disease. The introductory chapter is by Foster Kennedy. There are other important chapters on heredity, by A. Myerson; electrical activity of the brain, by Hallowell Davis and Pauline A. Davis; mental and emotional changes produced by diseases of the brain, by T. J. Putnam; effects of chemical and hormonal agents, by K. M. Bowman; of barbiturates and bromides, by F. J. Curran; of benzedrine, by W. Bloomberg; of Marihuana, by Walter Bromberg; physiologic changes in emotional states, by J. C. Whitehorn; psychotherapeutic effects by chemical agents, by Manfred Sakel. Why mental and emotional are repeatedly referred to as though separate, is not clear—the mental is formed by the emotional and intellectual. The Association's high scientific purpose is maintained in this book. There is a copious bibliography and an informative index. N. Y.

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MINERAL METABOLISM. By ALFRED T. SHOHL, M.D., Research Associate in Pediatrics, Harvard University (American Chemical Society Monograph Series). Pp. 384; 13 illustrations and 41 tables. New York: Reinhold Publishing Corp., 1939. Price, \$5.00.

THIS long awaited monograph fulfills the expectations of those acquainted with its preparation. It succeeds admirably in its discussion of the rôle of the various minerals in the structure and function of the human body. As the field of mineral metabolism is now the subject of vigorous investigation and is rapidly expanding, it is only to be expected that the presentation of certain fields is not completely up to date.

The material presented is selected from data gathered on human subjects, supplemented with discussions of experimental results upon laboratory animals wherever these data are important in arriving at an understanding of the normal physiology of the body. Pathologic material is used to illustrate variations from the mechanisms of the normal mineral metabolism. Instead of discussing all of the data upon each element within a single chapter, the material is scattered throughout the book, and only brief

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summaries and definite problems outlined in the chapters on the separate elements. This plan has been adopted because it is apparent that the interrelation, of the various elements among themselves, to water, acid-base equilibrium and body functions are so complicated that a clearer picture is obtained when physiologic function is made the center of discussion.

The mineral composition of the body as a whole and of its several parts is the first topic considered. In this is discussed the mineral composition of the various tissues at different periods of life, from the fetus to the adult. This is followed by a consideration of the volume and composition and excretions and their effects upon changing the rôle in mineral metabolism of the body fluids. Internal secretions and their rôle in mineral metabolism is the subject of another chapter. This is followed by chapters upon 1, total base, chloride, ammonium and bicarbonate; 2, calcium and magnesium; 3, phosphorus; 4, sulfur; 5, iron; 6, iodine and 7, trace elements. The chapters on iron and iodine were prepared by Dr. F. C. Bing.

The last third of the monograph is taken up with a discussion of water metabolism, and anion-cation relationships of the body as affected by the minerals of the food. In the concluding chapter the topic of mineral intake, balances and requirements are summarized.

There are relatively few errors typographical or otherwise. To everyone interested in the ubiquitous rôle of the various minerals in the physiologic economy of the human body this volume can be recommended highly. H. V.

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*DAS ANTLITZ DER BLINDHEIT IN DER ANTIKE. Eine medizinisch-kulturhistorische Studie.* By A. ALBERT M. ESSER, Dr. med. et phil. Pp. 178. Stuttgart: Ferdinand Enke, 1939. Price, Paper, Rm. 9.50; Bound, Rm. 11.00.

THE author has attempted, from a consideration limited to true source material, to unite the various points of view about blindness in antiquity. To this end he considers briefly the classical references illustrating the natural history of blindness, its social history (as a punishment, in wartime, accidental), its effect on the blind (prophets, poets, beggars), and the condition of blindness in various aspects. One unquestionably comes across some interesting allusions, but even with an indefinite amount of leisure time at one's disposal, it is doubtful whether even most careful study would adequately repay the average reader for the time spent. Perhaps an edition in Braille would evoke more enthusiastic responses. E. K.

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*BRUCELLOSIS IN MAN AND ANIMALS.* By I. FOREST HUDDLESON, D.V.M., M.S., Ph.D., Research Professor in Bacteriology, Michigan State College, East Lansing. Contributing Authors: A. V. HARDY, M.S., M.D., Dr. P.H., Associate Professor of Epidemiology, DeLamar Institute of Public Health, Columbia University Medical School, J. E. DEBONO, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta, and WARD GILTNER, D.V.M., M.S., Dr.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Pp. 339, with 40 illustrations (some in color). New York: The Commonwealth Fund, 1939. Price, \$3.50.

AN accurate, authoritative, and comprehensive book on *Brucella* infections in man and animals, this book is of value to laboratory workers, physicians, and veterinarians. The authors stress the difficulties which are often encountered in establishing a diagnosis of *Brucellosis* and helpful suggestions are offered as to the use and interpretation of various diagnostic procedures.

Under specific treatment the authors discuss their experiences with the use of Brucellin, which they believe to be of value in certain cases. The administration of mixed typhoid and paratyphoid vaccine intravenously is referred to briefly, but, in view of the experience of others, this form of therapy warrants more extensive discussion. Sulfanilamide is recognized as having given some promising results but as being far from a specific for Brucellosis.

No mention is made, under general therapeutic measures, as to the eradication of possible foci of infection, an item that we believe to be of some importance.

H. F.

#### NOMENCLATURE AND CRITERIA FOR DIAGNOSIS OF DISEASES OF THE HEART.

By the Criteria Committee of the New York Heart Association. ARTHUR C. DEGRAFF, M.D., CLARENCE E. DE LA CHAPELLE, M.D., CARY EGGLESTON, M.D., CHARLES E. KOSSMANN, M.D., ROBERT L. LEVY, M.D., JOHN B. SCHWEDEL, M.D., and HAROLD E. B. PARDEE, M.D., Chairman. Pp. 282; 52 illustrations. Fourth Edition. New York: New York Heart Association, a Division of New York Tuberculosis and Health Assn., 1939. Price, \$2.00.

THE present edition of this well known book shows considerable revision from the third edition and includes new material, notably a new section on Pathological Diagnosis.

It should be available to all who make cardiac diagnoses and should be read by all interested in heart diseases. It should be the primer of the new crop of heart specialists now coming on. The work has been well done and reflects great credit on the Committee. One cannot doubt that it will serve its chief purposes, which are to elevate the general standards of cardiac diagnosis and to bring about more uniformity of diagnostic nomenclature. Even those sturdy survivors of a happier era who object to being standardized will probably find few grounds for quarrel with the Committee.

C. W.

#### VIRUSES AND VIRUS DISEASES (LANE MEDICAL LECTURES) (Stanford University Publications, University Series, Medical Sciences, Vol. IV, No. 1).

By THOMAS M. RIVERS, M.D., Sc.D., Director, Hospital of the Rockefeller Institute for Medical Research, New York City. Pp. 133; 34 illustrations. Stanford University: Stanford University Press, 1939. Price, Paper, \$1.75; cloth, \$2.50.

OF the five lectures of this series of the well known Lane Medical Lectures, the first is devoted to lymphocytic choriomeningitis, presenting the clinical picture of the first patient from whom the virus was obtained and the manner in which the virus was shown to be the cause of the malady. Lecture two concerns the pathology of viruses in which the cytoplasmic inclusion bodies of fowl-pox, molluscum contagiosum, psittacosis, vaccinia, trachoma, rabies, infectious myxomatosis of rabbits and tobacco mosaic are found. The lecturer reiterates that hyperplasia, hyperplasia followed by necrosis and necrosis are the primary characteristic pathologic changes in all virus maladies. Inflammation is regarded as secondary. Shope's papilloma of rabbits and Rous' sarcoma of fowl are cited as the etiologic factors of certain malignant growths; no mention was made of Lucke's tumor of frogs. The third lecture is devoted to the fundamental principles of immunology and serology which are operative in virus diseases as in all fields of biology. The nature of viruses, in lecture four, is considered in the light of such studies as the determination of size of the particle by filtration, centrifugation, diffusion or direct measurement of the particle; the shape of the particles; density and electric charge. Purification of viruses, cultiva-

tion, mutation and the antigenic properties of viruses are briefly mentioned. The last lecture is devoted to the treatment and prevention of virus diseases in which the use of drugs, vaccines and convalescent sera were discussed. In the case of chemotherapy the lecturer found the reports few and discouraging, likewise, convalescent serum therapy was of doubtful efficacy. Vaccination against virus diseases has been the most successful method of combat but much still has to be learned about this method of treatment.

H. M.

**CLINICAL TOXICOLOGY.** By CLINTON H. THIENES, M.D., PH.D., Professor of Pharmacology and Head of the Department of Pharmacology, School of Medicine, University of Southern California, Los Angeles; Attending Pathologist (Toxicology), Los Angeles County Hospital. Pp. 309; 7 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$3.50.

This book is written essentially in the manner of a compendium with the primary purpose of serving as a classroom text or simple guide for the general practitioner. As such, it may be useful. The list of drugs and poisons appears to be comprehensive, however only the essentials pertaining to them are treated. The last sixth of the book is devoted to the chemical diagnosis of poisoning. In this section are given methods of analyses in more or less cook-book style without attempt at any chemical evaluation.

F. S.

**VITAMIN D. Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations.** By C. I. REED, A.M., PH.D., Associate Professor in Physiology, H. C. STRUCK, M.S., PH.D., Associate in Physiology, and I. E. STECK, M.S., M.D., Instructor in Physiology and in Medicine, Department of Physiology and Department of Medicine, College of Medicine, University of Illinois, Arthritis Clinic, Illinois Research and Educational Hospitals. Pp. 389; 13 illustrations and 36 tables. Chicago: The University of Chicago Press, 1939. Price, \$4.50.

This book has evolved from the investigations of the authors on the physiology and therapeutic applications of vitamin D. It is perhaps a little overbalanced on the personal side. On the other hand it contains an excellent review of recent literature (1926-1939) which is enlivened by personal interpretation and discussion. Each chapter is well summarized and there is a 48-page bibliography.

E. W.

#### NEW BOOKS.

*Obstetrics and Gynecology.* In two volumes. By the Departmental Staff of the University of Chicago and Other Contributors. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology in the University of Chicago; Chief of Service, The Chicago Lying-in Hospital, Chicago. Pp. Vol. 1, 1000; Vol. 2, 1031; illustrations, Vol. 1, 359 and 14 plates, Vol. 2, 304 and 10 plates (plates mostly in color). Philadelphia: Lea & Febiger, 1940. Price, \$20.00 set.

*The Malarial Therapy of General Paralysis and Other Conditions.* By WILLIAM H. KUPPER, M.D., Formerly Resident Physician, Florida State Hospital and Special Physician Associated with the Station for Malaria Research, International Health Division of the Rockefeller Foundation, Tallahassee, Florida. Pp. 155 (lithoprinted); illustrated. Ann Arbor: Edwards Bros. Inc., 1939. Price, \$2.25.

*The New International Clinics, Vol. 1, N.S. 3, 1940.* Edited by GEORGE MORRIS PIERSON, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. With 17 Collaborators. Pp. 319; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The 6 original contributions are on as many widely separated subjects. The 12 "clinics" are from various services of the Hospital of the University of Pennsylvania. The 87-page of recent progress is on the vitamins by Cantarow.

*Fetal and Neonatal Death.* A Survey of the Incidence, Etiology and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life. By EDITH L. POTTER, M.D., Ph.D., Instructor in the Department of Obstetrics and Gynecology, The University of Chicago; Pathologist at The Chicago Lying-in Hospital, and FRED L. ADAIR, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, The University of Chicago, and The Chicago Lying-in Hospital. Pp. 207; 31 illustrations. Chicago: The University of Chicago Press, 1940. Price, \$1.50.

*A Doctor's Holiday in Iran.* By ROSALIE SLAUGHTER MORTON, M.D., Author of "A Woman Surgeon." Foreword by Surgeon-General HUGH S. CUMMING (Retired). Pp. 335; illustrated. New York: Funk & Wagnalls Company, 1940. Price, \$3.00.

*Dermatologic Allergy.* An Introduction in the Form of a Series of Lectures. By MARION B. SULZBERGER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending in Dermatology and Syphilology, Montefiore Hospital, New York, etc. Pp. 540; 39 illustrations, 13 color plates and 17 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, \$8.50.

*Practical Bedside Diagnosis and Treatment.* By HENRY JOACHIM, M.D., Chief-of-Medicine, Israel-Zion and Beth Moses Hospitals; Director of Medicine, Cumberland Hospital and Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, etc. Pp. 828. Springfield, Ill.: Charles C Thomas, 1940. Price, \$7.50.

*Essentials of the Diagnostic Examination.* By JOHN B. YOUMANS, B.A., M.S., M.D., Associate Professor of Medicine and Director of Postgraduate Instruction, Vanderbilt University Medical School. Pp. 417; 36 illustrations (some in colors). New York: The Commonwealth Fund, 1940. Price, \$3.00.

*Congenital Malformations.* A Study of Parental Characteristics with Special Reference to the Reproductive Process. By DOUGLAS P. MURPHY, M.D., F.A.C.S., Assistant Professor of Obstetrics and Research Associate in the Gynecologic Hospital Institute of Gynecologic Research, University of Pennsylvania, Philadelphia. Pp. 98; 7 figures, 55 tables and 1 photograph. Philadelphia: University of Pennsylvania Press, 1940. Price, \$2.00.

*Lee on the Levee* (An Historical Novel). By RALPH CANNON. Pp. 188. New York: The Saravah House, 1940. Price, \$2.50.

*The Medical Clinics of North America, Vol. 24, No. 2 (Cleveland Clinic Number—March, 1940).* Pp. 290; 39 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This Cleveland number contains a symposium of 9 articles on headache, and 15 on miscellaneous subjects.

*Artificial Pneumothorax.* Its Practical Application in the Treatment of Pulmonary Tuberculosis. Contributions by Saranac Lake Physicians to the Studies of the Trudeau Foundation. Editorial Committee: EDWARD N. PACKARD, M.D., JOHN N. HAYES, M.D., and SIDNEY F. BLANCHET, M.D. Foreword by E. R. BALDWIN, M.D. Pp. 300; 85 illustrations and 33 tables. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

*Accepted Foods and Their Nutritional Significance.* Containing Descriptions of the Products which Stand Accepted by the Council on Foods of the American Medical Association on September 1, 1939. Pp. 492. Chicago: American Medical Association, 1939. Price, \$2.00.

*Chemisches Praktikum für Mediziner.* By DOZENT DR. HANS BODE, Kiel, und PROF. DR. HANS LUDWIG, Danzig. Pp. 131. Wien: Franz Deuticke, 1940. Rm. 4.

*The Newer Nutrition in Pediatric Practice.* By I. NEWTON KUGELMASS, B.S., M.A., M.D., PH.D., Sc.D., Attending Pediatrician, Broad Street Hospital and Heckscher Institute, New York; Consulting Pediatrician, Lynn Memorial, Monmouth Memorial and Muhlenberg Hospitals, New Jersey, etc. Pp. 1155; 183 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, \$10.00.

*Die akute Myokarditis.* Klinische und pathologisch-anatomische Beobachtungen bei 36 Krankheitsfällen in ihren Beziehungen zu Herd-Infekten, zu Allgemein-Infekten (Grippe) und zur Tuberkulose. By FERDINAND WUHRMANN, Oberarzt der Klinik. Pp. 148; 86 illustrations. Basel: S. Karger A.-G., 1939. Price not given.

*Sleep and Wakefulness as Alternating Phases in the Cycle of Existence.* By NATHANIEL KLEITMAN, Department of Physiology, The University of Chicago. Pp. 638; illustrated. Chicago: The University of Chicago Press, 1939. Price, \$5.00.

#### NEW EDITIONS.

*Elmer and Rose Physical Diagnosis.* Revised by HARRY WALKER, M.D., F.A.C.P., Associate Professor of Medicine, Medical College of Virginia, Richmond. Pp. 792; 295 illustrations. Eighth Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$8.75.

*The Pathology of Internal Diseases.* By WILLIAM BOYD, M.D., LL.D., M.R.C.P., Ed., F.R.C.P., Lond., DIPL., PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 874; 353 illustrations and 4 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$10.00.

*Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord.* A Concise Introduction to the Principles of Localization of Diseases and Injuries of the Nervous System. By ROBERT BING, Professor of Neurology, University of Basel, Switzerland. Translated and edited by WEBB HAYMAKER, Assistant Clinical Professor of Neurology and Lecturer in Neuro-Anatomy, University of California. Pp. 292; 125 illustrations (27 in color), and 7 plates. Eleventh Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$5.00.

A new and enlarged edition of a most excellent work. The concise and graphic presentation of a difficult and important subject. Strongly recommended as an authoritative reference for all practitioners other than neurologists.

# PROGRESS OF MEDICAL SCIENCE

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## THERAPEUTICS

UNDER THE CHARGE OF

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### THE RATIONALE OF AMPHETAMINE (BENZEDRINE) SULPHATE THERAPY.\*

Any new pharmacologic preparation which has unusual effects is immediately used in a wide variety of conditions in the hope of achieving new and unusual therapeutic results. This has been the fate of amphetamine sulphate, and the time has come to review its physiologic and psychologic effects in order to determine the rationale of its proper application in medicine.

A comprehensive study of the fundamental pharmacology of amphetamine sulphate will be found in the report of the Council on Pharmacy and Chemistry.† Alles is mainly to be credited with the development of the pharmacologic physiology of this drug, and it is to his papers and those of Barger and Dale, Chen and Meek that the reader is referred for those fundamental studies which demonstrate the general sympathomimetic character of amphetamine sulphate. The effects of amphetamine sulphate may be divided into two main groups.

**Sympathomimetic Effects.** These may be briefly summarized as follows: Sympathomimetic drugs in general relax the smooth muscle of the viscera, but also constrict the smooth muscle of the arterioles so that the blood pressure is raised. This general formula can be worked out into its details as follows:

1. Amphetamine sulphate dilates the pupil of the eye, widens the palpebral fissure, increases the intra-ocular tension and lessens the power of accommodation. In these properties it resembles its synergist,

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† J. Am. Med. Assn., 109, 2064, 1937.



atropine; although its action is slower, less violent, of shorter duration, and more easily overcome by prostigmin and mechohyl.

2. The gastro-intestinal tract: amphetamine sulphate tends to relax the musculature of the gut and in general delays the rate of movement of bismuth and of food. That is, it reduces peristalsis.

On the genito-urinary tract it has characteristic sympathetic effects. Thus, it relaxes the entire genito-urinary tract insofar as present studies have proceeded; viz., it enlarges the kidney, dilates the pelvis and the calyces, dilates the ureter, and produces a characteristic dilatation of the bladder.

3. The blood pressure: the effect of amphetamine sulphate is to raise the blood pressure, whether given by mouth, intramuscularly or intravenously. The rise is marked and lasts from 1 to 2 hours in the human being. The effect tends to lessen and disappear after the drug is used over an extended period of time.

Amphetamine sulphate does not have a pronounced effect on the cardiac muscle as demonstrated by the electrocardiograph. The pulse rate tends to be somewhat slowed, and in this respect amphetamine sulphate is not sympathomimetic in effect.

It is noteworthy that all of these effects are produced only by large doses of the drug; 10 mg. given by mouth, or otherwise, produces very little sympathomimetic result. It ordinarily takes from 20 to 30 mg. to raise the blood pressure in appreciable measure and to relax the gastro-intestinal tract or to dilate the genito-urinary tract. The eye effects are produced by instillation of a solution varying anywhere from 0.5 to 2%.

4. Generally speaking, the sympathomimetic drugs reduce nasal mucous secretion, dry up the salivary secretion, and reduce sweating. This is true of adrenalin, ephedrine, amphetamine sulphate, paredrine, propadrine and the wide variety of new sympathomimetic drugs which have been introduced. Amphetamine sulphate reduces the salivary secretions and definitely lessens sweating. These effects usually follow large doses but are also obtained with doses of 2 to 5 mg. in exceptionally susceptible people. Benzedrine Inhaler and Benzedrine Solution have long been used for topical application in counteracting rhinorrhea.

**Wakeful-Psychologic Effects.** The second group of effects is that which is here termed the wakeful-psychologic effects. In this respect amphetamine sulphate is in a class by itself, insofar as the sympathomimetic drugs are concerned. Adrenalin does not produce these effects; ephedrine produces them only in minor degree; paredrine and propadrine do not evoke them at all. The wakeful-psychologic effects, therefore, have no relationship to any of the other effects of amphetamine sulphate, those which have here been termed sympathomimetic. This effect is *sui generis*, a specific amphetamine sulphate result.

Normal sleep may be profoundly interfered with by amphetamine sulphate. A sense of wakefulness is produced which is the very antithesis of drowsiness. In its pleasant aspect, the psychologic effect is that of increased vigor and enhanced pleasure in every direction with a feeling of increased power physically and mentally. When an unpleasant degree is reached, the psychologic effect goes on to a feeling of being too alive, over-responsive to the environmental influences, and a

sense of unpleasant threatening excitement ensues. This effect on sleep and mood has been widely studied. It was the first important therapeutic application of amphetamine sulphate if we except from consideration its local rhinologic use.

Some interesting but not completely substantiated work has tended to show that amphetamine sulphate increases the intelligence score under test conditions. Molitch and Eccles, Sargant and Blackburn corroborate this; while Meerlo, McNamara and Miller do not agree with the findings. It is also stated that this drug increases psychomotor skill (Thornton *et al.*). There is no questioning the fact that with the experimental animal and in the relatively large doses given, there is an enormous increase of activity which, however, is not productive and seems almost maniacal in its manifestations. It is a common experience in my laboratory to witness the mutism of dementia precox disappear for a short time after the injection of 30 mg. of amphetamine sulphate. This result, however, is temporary and of no therapeutic value. Irrespective of usefulness, the drug is profoundly effective in producing a wide group of psychologic reactions, mainly in the direction of excitation.

It is, therefore, to be kept definitely in mind in the use of amphetamine sulphate therapeutically that there are these two groups of effects to be taken into account: first, the general sympathomimetic reactions, and second, the wakeful-psychologic effects which are the specific characteristics of the pharmaceutical, and are obtained even with small doses, from 1 to 10 mg. These are related to some unknown central stimulation concerning which I wish to theorize at this point.

**Rest-recuperative and waking-activating mechanisms:** There is some relatively obscure mechanism by which activities of a purposive and conscious type are brought to a standstill and which are associated with a feeling of fatigue and drowsiness, and which eventuate in sleep. This may be called the rest-recuperative mechanism. Disorder of this mechanism is very common and especially in the neuroses.

Less well known and, in fact, not at all emphasized in the discussion of the normal cycles of existence, is what may be called the *waking-activating* mechanisms, by which after sleep or after rest the organism re-prepares itself for activity, manifesting this on the conscious psychologic level by a feeling of alertness and a desire for activity. This is also impaired in many conditions and especially on a functional level in the neuroses. In fact, the essential disturbance of most neuroses resides in the impairment of the rest-recuperative and the waking-activating mechanisms.

How does the foregoing discussion link itself up with the therapeutic uses of amphetamine sulphate? These uses are considered, first, in relationship to the specific effects of the drug, and second, in relationship to its sympathomimetic activities.

**Specific Effects.** 1. The effect in counteracting sleep has brought about the use of amphetamine sulphate as a specific in narcolepsy. This has been well established by a number of workers (Prinzmetal and Bloomberg, Ulrich). Suffice it to say that the long-continued use of the drug in considerable dosage (30 to 50 mg. per diem) does not seem to produce ill-effects in these patients, nor does the drug seem to lose its effects finally, as is the case so often when drugs have to be

used over a long period of time. Amphetamine sulphate does not cure narcolepsy, but it produces a symptomatic relief of such magnitude as to entitle it to be designated a symptomatic specific.

2. There has developed a general use of amphetamine sulphate to offset sleep and fatigue whenever something extraordinary has to be performed, during a period in which sleep or fatigue would be disastrous or non-desirable. Thus, people who have to drive a long distance and especially at night are apt to take amphetamine sulphate to keep them awake. Students preparing for examinations are notorious users of the drug in order to offset the fatigue of continued "grinding" through the night. Students also use it to sharpen their association processes and to increase their mental capacity during the examination itself. These are not wholesome uses of the drug. It is not wise to disturb the sleep and resting process by any drug. It is not wise to rely upon a drug for the ability to pass examinations. Self-administration to meet emergencies of this type is against good hygiene and represents an abuse of this chemical.

There are social and personal circumstances where to fall asleep or to suffer with temporary fatigue would be disastrous in a somewhat imperfect world. Under these exceptional circumstances 5 to 10 mg. of amphetamine sulphate does no harm and meets a trying situation better than any other chemical of the present-day pharmacopœia. It is fair to state at this point that the sale of the drug is now restricted to prescription use only, and that the abuses noted above are thus bound to disappear.

3. The drug is useful in counteracting poisoning by the barbiturates. The drop in blood pressure, as well as the unconsciousness, are offset. The best method for using the drug under such occasions is either by subcutaneous injection or in the emergency by intravenous use. Large doses are here required, from 20 to 30 mg. being safe if given very slowly and in sufficient dilution. If the drug is to be used intravenously, it is wise to dissolve 30 mg. in 10 cc. of water and inject it over a period of 10 minutes, just as one would give sodium amytal intravenously.

4. Linked with this relationship of amphetamine sulphate to the barbiturates is what is elsewhere called their "reciprocal pharmacology." If one desires to obtain a sedative effect with the barbiturates and seeks to avoid the hang-over and the depression which these drugs tend to produce, the addition of small doses of amphetamine sulphate is of value. Thus, the drugs may be used simultaneously, and the sedative effect of 3 grains of sodium amytal may be modified in pleasant manner by 10 mg. of amphetamine sulphate. The specific amphetamine sulphate effect is not then produced, but the chemical offsets the disagreeable torpor and depression of amytal. If phenobarbital is used for sedative therapy, the narcotization of 1 grain of this drug can be offset by from 5 to 10 mg. of amphetamine sulphate.

Especially valuable is this conjoined use when phenobarbital is used in the treatment of epilepsy. Often in such treatment the effects of phenobarbital become oppressive, so that while the attacks may be diminished or abolished there is a very disagreeable slowing up of the thought processes and general unpleasant phenobarbital reactions. These may be offset without any effect whatever of untoward type on

the attacks by the addition of appropriate amounts of amphetamine sulphate. Usually a small amount will suffice. It has been definitely shown by Merritt and Putnam that amphetamine sulphate does not increase the epileptic attacks. Personal work tends to show that whatever effect amphetamine sulphate has on epilepsy is ameliorative rather than injurious.\*

5. It has been shown by certain workers (Bloomberg, Reifenshtein and Davidoff) that the effects of acute alcoholism may be offset by amphetamine sulphate. Bloomberg believes that a certain number of chronic alcoholics may be treated by this drug. The rationale for its use in these cases is quite simple and clearly logical as well as pharmacologic. Alcohol is a narcotic, tending to produce sleep and torpor and it is perfectly in line with the pharmacology of amphetamine sulphate that it counteracts this effect. In the treatment of the chronic alcoholic it is of some value because, when taken in the morning, it lifts up the mood sufficiently so that the desire for alcohol is diminished, since the chronic alcoholic uses the temporary lifting effects of alcohol as the basis for his continued indulgence. It is not meant to imply here that amphetamine sulphate is a specific drug in the treatment of alcoholism. It is here stated, however, that both from the literature and from personal experiments, it has some value in counteracting acute alcoholism. In the treatment of the chronic alcoholic one must beware of pharmacologic magic. Alcoholism is more than chemistry or vitamins. Whatever value any drug may have, it must be merely an adjunct to psychology and social reorganization as well as to more far-reaching physiologic measures.

6. Of importance is the discriminating use of the drug in the treatment of the neuroses. Whether it is to be of value or not can be readily determined in each individual case by the use of small doses on arising and throughout the morning. If the effect is favorable, in that the patient feels better, has a greater aptitude for activity, an enhanced pleasure in existence, then the drug *together with other measures* should be used. On the other hand, if the patient becomes jittery, shows increased agitation, becomes more depressed after a few doses, the drug is of no value whatever and should be immediately withdrawn. It is by no means valuable in most depressions. It does not seem at present to be of importance by itself in the treatment of the psychoses. In the severe neuroses it has only a limited range of usefulness.

On the other hand, in transitory or short neurotic states, especially of the reactive type, where the individual is finding it difficult to meet a situation and is reacting by a mood disturbance as well as by lessened activity, the drug is apt to have great value if given in small doses. Even in such cases amphetamine sulphate is more apt to help if the patient is given sedation at night than if it is used by itself. In other words, the corrective pharmacology of amphetamine sulphate in relationship to the barbiturates and to the sedatives can be capitalized by its judicious use in the treatment of the neuroses.

7. Obesity: The logic of the use of amphetamine sulphate in this condition is two-fold. First, in the case of many individuals it lessens appetite (Nathanson). This is probably due to the relaxing of the

\* Cohen, B., Showstack, N., and Myerson, A.: J. Am. Med. Assn. 114, 480, 1940.

bowel and the diminution of hunger contractions under its use. Secondly, by increasing the desire for activity a greater capacity for exercise and physical exertion is brought about. Obviously, obesity is treated by a reduction of the intake of food and by increase of the activities. Amphetamine sulphate has a definite value in both these directions, although it is by no means a specific nor has it any value where diet regulation is not prescribed or followed, and where the general hygiene of the individual is defective. As stated elsewhere, no drug takes the place of hygienic living and of proper alimentation.

8. **Parkinson's Disease:** The drug has been accepted by the Council on Pharmacy and Chemistry as a useful adjuvant to the treatment of Parkinson's disease. Combined with stramonium (which is an atropine derivative and therefore a natural synergist of amphetamine sulphate), it is probably useful in giving temporary relief, since no treatment has any permanent value in this condition. Care should be used not to give this combination in such amounts that excessive drying of the mouth takes place.

**Sympathomimetic Effects.** We come now to the effects of amphetamine sulphate as a sympathomimetic drug.

1. The Council on Pharmacy and Chemistry has accepted its use in Roentgen ray work to overcome spasm and thus make it possible to take better Roentgen ray pictures of the gastro-intestinal tract. This use it shares with other drugs of the same type.

2. I do not believe the drug has much, if any, value in spastic colitis or in generalized spastic states of the gastro-intestinal tract. The organism probably becomes quickly adjusted to the drug; the effects wear off; and they are of too short duration to be useful. Furthermore, the amount of amphetamine sulphate necessary to produce a good relaxation of the gastro-intestinal tract is too great for repeated and constant use. I think it can safely be said that whatever value it has in the treatment of this condition is temporary and can only be purchased at too high a price of sympathetic stimulation.

3. In certain cases of spasm of the genito-urinary bladder, the drug has definite value, whether the spasm be organic or functional in origin. It is usually wise to combine it in such cases with the barbiturates.

4. On the eye, amphetamine sulphate is a useful mydriatic, especially if combined with other drugs. For this I refer the reader to the writings of Beach and McAdams, Myerson and Thau, and others. The value of the combinations used lies in the fact that a quick dilatation is produced which does not last too long and which can easily be offset by prostigmin or any of the parasympathetic drugs.

**Contraindications for the Use of Amphetamine Sulphate.** 1. Any powerful chemical used in the treatment of the human being finds individuals who have idiosyncratic reactions to it and who are over-responsive in a disagreeable or even dangerous way. This is true not alone of amphetamine sulphate but of digitalis, morphine, codeine, cocaine, hyoscine. The most common disagreeable or dangerous reactions are a sense of fullness in the head together with severe headache, a sense of giddiness, extreme excitement and irritability, a dry feeling in the mouth with queer sensations throughout the abdominal region. In some indi-

viduals the appetite is completely destroyed. In others there is extreme constipation. It is wise to test out the drug in small doses first. The idiosyncrasies in reaction are usually immediate.

2. Amphetamine sulphate should not be used where sleeplessness is a prominent symptom except in combination or in association with sedatives. Where there is intense agitation or great anxiety, it is usually of no, or little, value and often increases the agitation and excitement. Its value in any mental state can be quickly determined, as stated above, and the drug should be discarded immediately if the effects are to increase the unpleasant emotional state of the individual.

3. It is best not to use the drug wherever there is hypertension and cardiac disease. Certainly it should not be used in doses beyond 5 to 10 mg. in such situations, and in general it may be stated that there are stimulants which are better borne than amphetamine sulphate wherever cardiovascular disease is present. It is wise to state here that the individual reaction even in cardiac disease may be very variable and that a cautious testing out is productive of no harm. The drug should be immediately withdrawn if pain and cardiac irritability follow. The blood pressure is not affected in therapeutic doses.

4. Amphetamine sulphate should not be used where there is marked atony of the gastro-intestinal or of the genito-urinary tracts. Its sympathomimetic effect is to increase these conditions. Very small doses will not make any particular difference in respect to the visceral atony, but even moderate doses will greatly increase the disability of the viscera.

**Habit Formation.** During 4 years of steady use on a large number of patients, I have seen little evidence that the drug is to any great extent habit-forming. The drugs which produce a constant repetitive desire are the narcotics—morphine, codeine, cocaine, alcohol. It is rare to see anyone who has become addicted to strychnine. There are few people who become caffeine habitués, although many use too much coffee. Those people whom I have encountered who have found themselves unable to break away from the use of amphetamine sulphate have been those who have had chronic, otherwise incurable, narcoleptic or depressive mental states. They have, on the whole, been better off with the drug than without it. Their addiction has largely taken on the picture of a deficiency addiction; that is, they have been impelled to take the substance continuously because something is lacking in the organism which the drug supplies. *Furthermore, there are no injuries to personality or intelligence, such as take place with the narcotic drugs.* The constant user of amphetamine sulphate does not lie or steal or show deterioration in any way. It is possible he may be doing his organism damage by its use; in small doses, however, I have seen no evidence of this taking place. Whenever a patient takes large doses, the *unpleasant* results usually put an end to the habit.

In other words, there is not much danger of drug addiction. There is much unwise use, some administration for unhygienic purposes, such as its use by students, automobile drivers, alcoholics who want to drink more than they should, and so on. These are the liabilities of a drug

which has, on the whole, many important assets for the successful and judicious practice of medicine.

ABRAHAM MYERSON, M.D.\*

The generosity of the Smith, Kline & French Laboratories in supplying amphetamine sulphate is hereby gratefully acknowledged.

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## RADIOLOGY.

UNDER THE CHARGE OF  
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## FLUOROGRAPHY.

**Historical.** Fluorography (miniature radiography, indirect radiography or Roentgen photography) is photography of a still image produced by Roentgen rays on a fluoroscopic screen. The image is photographed through a light proof space with a camera having a large aperture lens.

The whole history of the Roentgen rays ( $x$ -ray) contains references to attempts to make use of the photographic method of reproducing the roentgenoscopic image. Hirsch<sup>4</sup> pointed out that Roentgen, in his first paper concerning the discovery of the new light to which he gave the name of "X-ray," demonstrated the fluorescent and photographic effects of these rays. Since that time much ingenuity has been shown in the efforts to establish the best technical method of recording the Roentgen image. "The screen image, simple and easy in its attainment, instantaneous in its appearance, graphic in its visibility, seemed for the moment to be the most desirable and it was only logical to attempt to obtain a permanent record of this image by ordinary photography." Hirsch credited Bleyer with making the first attempt, in April, 1896, to construct and use an apparatus for photographing the fluorescent image. "Porcher (1897)," he stated, "after considerable experimentation, discarded the method as impractical and as having no advantage whatever over direct roentgenography." "However," Hirsch continued, "the allure of the moving picture stimulated workers to investigate the possibility of an indirect method of its accomplishment and in 1907 Köhler, who was engaged in direct Roentgen cinematography, men-



tioned photography of the fluorescent image as a promising future possibility, and in 1909, in association with Biesalski, described a practical method of fluoro-roentgenography, utilizing a screen of calcium tungstate (blue fluorescence), a camera with an F 2.0 lens and a mirror which permitted placing the camera outside the beam of direct radiation. Biesalski also used a concave mirror instead of a lens by means of which he could obtain a much greater effective optical aperture.

"It was apparent that the future development of the method depended on the possibility of obtaining lenses of greater aperture, screens of brilliant luminescence and photographic films of high sensitivity." Cole and Leven, in the United States, and Comodon in France in 1909 and 1910 were credited by de Abreu<sup>1a</sup> with at least touching on the principles involved in indirect roentgenography (Roentgen photography) in their remarkable trials with Roentgen cinematography. Hirsch stated that "Caldwell in 1911 presented all the basic and essential principles underlying the application of fluorography and foreshadowed its present-day application with prophetic instinct and scientific acumen. He used a 4 by 5 camera with a Cooke lens, working at aperture F 4.5 and a 'Gehler folie' screen which had phosphorescent (after glow) as well as high actinic fluorescence." He experimented to determine whether the "after glow" would interfere with making successful photographs of the screen in rapid succession and demonstrated it was not of practical importance as a contaminating factor. The photographs he obtained of the extremities, the thorax and the thoracic contents were full of rich detail and, as he had hoped, the camera recorded much more than the eye could see on the fluorescent screen. "Caldwell," Hirsch asserted, "pointed out the advantages of the method, the low cost, the simplification of the problem of filing and transportation. He prophesied that with the development of screens of higher actinic properties, photographic films of greater sensitivity, lenses of greater speed and more intense excitation by roentgen rays, the method would attain a great practical value and would revolutionize roentgenography." Hirsch continued his historical review with the statement that Loman and Camandon used an F 1.55 lens with a specially sensitized film; Luboshez made use of an F .625 lens and still more recently Dariaux and Dijan, a lens aperture F .53; Schinzel suggested the use of a screen bent into a surface concave toward the lens for patients to correct for some of the optical errors of the wide aperture lenses. The great improvement in recent years in fluorescent screens by Leonard Levy of London and in photographic materials, Hirsch considered responsible for the development of the method to such a state that its practical and routine application was now possible.

**Practical Application.** Hirsch credited de Abreu (Brazil) with the first large scale application of the method. The researches of de Abreu and his group were commenced in 1924<sup>1b</sup> and were related to the utilization of an inexpensive process of mass survey work in examination for pathologic processes involving the thorax and its contents. The first Thoracic Census Centers were installed at Rio de Janeiro at the end of 1936 and the beginning of 1937. Original research along the same lines was started in South Africa in 1927 at the department of roentgenology of the Witwatersrand Native Labour Association. Work was being done on similar lines independently at that time in Germany and

Japan. Dormer and Collender,<sup>2</sup> who carried out the work in South Africa, stated that impetus was given to their efforts by a desire to produce facsimiles of roentgenograms of large groups, a proportion of which possibly exhibited pathologic processes involving the thoracic cage or its contents, economically and rapidly. They set as a goal the examination by this method of 2000 or more persons each day with a suitable plant. Using miniature film (approximately 35 mm.) they found the cost, the film and the processing considered, to be at least one-twentieth that of roentgenographic examination, using 12 by 15 inch (30.5 by 37.5 cm.) films. They considered the method particularly applicable to the examination of groups of persons, for example, recruits in military mobilization, as an adjunct in the physical examination of school children, the inhabitants of native locations, and the personnel of mine compounds and reserves. As a clinical accessory it made possible the investigation of contacts and suspects in campaigns directed toward the prevention and cure of tuberculosis on a much wider scale than otherwise because of its inherent economy. These authors found this new method of examination to be a rapid and inexpensive method of separating the abnormal from the normal in routine investigation of the thorax and its contents. They found it also had considerable value in affording a permanent graphical record of progress of the changes consequent to the establishment of an artificial pneumothorax or other form of collapse therapy. Although they personally had not used the method for such purposes, they prophesied that it would prove equally valuable in control of fractures and in recording the roentgenoscopic image of the esophagus, stomach, small bowel and colon after the ingestion of an opaque medium and after the use of the opaque enema in examination of the large bowel. The most brilliant demonstration of the value of this new method of using the Roentgen rays as an ally in clinical investigation was and is being carried out in South America. The interest of de Abreu and his co-workers<sup>6</sup> in this subject commenced in 1918 and was renewed in 1924. They attacked this problem diligently but were unable to obtain decisive or practical results.

They inaugurated the installation of the first fluorographic apparatus for the purpose of carrying out a collective thoracic survey at the German Hospital of Rio de Janeiro in 1936. In 1937 three additional centers were operating, one in the Public Health Department of Rio de Janeiro, one in the Navy Hospital and one in the Public Health Department of Victoria. In 1939 twenty-five fluorographic apparatus of this type had been installed in Brazil and many others in Argentina, Chile, and Uruguay.

The objections with which de Abreu and his co-workers had to contend at the beginning of their work were principally that since the initial roentgenologic indications of tuberculosis were very vague, fluorography would not show sufficient detail to make possible the recognition of an early lesion of tuberculosis. Experience proved to them that frequently Roentgen photography or fluorography which allows the making of fluorograms with the patient at various angles in relation to the beam of Roentgen rays, such as anterior and posterior descending directions, had an advantage over teleroentgenography, the present method commonly used, in the delineation of faintly visible lesions or even lesions that might be invisible in the teleroentgenogram.

In their opinion, the diagnosis of all or almost all cases of pulmonary tuberculosis with the aid of fluorography will assist in directing the social campaign against pulmonary tuberculosis to meet the threat presented by the individual. The social status of individuals who present a hazard and of those who are menaced by exposure would be known to the health authorities. The thoracic census survey would permit early diagnosis by means of Roentgen photography of all the population and enable the dispensaries to operate with the utmost efficiency. Systematic prophylaxis would at once solve the problem regarding suspects in private homes, whether they were members of the family, relatives, servants or visitors. These persons would be summarily withdrawn from contact with children and adolescents. The methods of sanitation and prophylaxis, based on hospital dispensaries, which were in vogue until the time of the inauguration of this new method, have failed because a complete thoracic survey had not been made. Tuberculosis prophylaxis, de Abreu and his co-workers contended, cannot be secured by treatment and isolation of a small percentage of persons suffering from tuberculous infection. On the contrary, it must be based on the discovery of all persons harboring infectious tuberculous foci and isolation of these for the protection of those in a receptive condition and threatened by tuberculous infection.

In a summary of the comparative costs of the examination of groups of persons, based on their experience with all methods, they estimated that routine roentgenographic examination by the methods commonly in use up to the time of the introduction of fluorography would entail an expenditure of \$900,000 per million examinations; roentgenoscopy (fluoroscopic observation) alone, which has been tried to reduce costs where economy demanded it, would cost \$340,000; while fluorography of the same number of persons could be accomplished with an expenditure of only \$112,000. In fairness to these figures it must be pointed out that the figures for roentgenographic examination quoted, apparently were based on the use of a single film for each examination. Had stereoscopic sets been made, as is done in some routine examinations, the film cost alone, without consideration of that of equipment and processing would have closely approximated \$1,500,000 instead of \$900,000.

A method of routine investigation of the thorax which in their experience has proved adequate for all the purposes for which it was suggested, at a minimum of 12.4% of the cost of other methods in use to that time prompted this summary of the experience of de Abreu<sup>1a</sup> on behalf of himself and his group: "Today, three years after the first practical results were achieved, collective fluorography is universally accepted. At the beginning of this work, there were many roentgenologists who expressed themselves in opposition to the procedure but have since become convinced as to its practicability."

The method was carried to the United States by Lindberg, who tried this method in the Macon County Tuberculosis Sanatorium at Decatur, Illinois, after a visit to Rio de Janeiro, late in 1937. De Abreu<sup>1a</sup> asserted that an attempt to interest American manufacturers in the construction of apparatus to carry out his method was unsuccessful.

Lindberg,<sup>8</sup> in a publication suggesting modifications of technique for Roentgen photography made in 1939 considered the method sufficiently

adequate for routine investigation, with the reservation that direct roentgenography be used to supplement this examination whenever abnormal densities were encountered. He considered the method definitely superior to roentgenoscopy by reason of the permanence of record, greater contrast and opportunity for more leisurely study and more deliberate interpretation.

Hirsch presented in detail a description of the apparatus and technique required for the production of the fluorograms on 35 mm. film. Different methods are suggested to prepare the fluorograms for viewing; they may be viewed with the aid of a magnifying glass, or they may be projected to a magnification of preferably 6.8 times. For the average chest, this just compensates for the distortion due to the use of 30 inch (76 cm.) target-screen distance. A good projector and a grainless screen are necessary for optimal results. The film may be projected to the usual full size lecture hall screen. The preferable method of filing and storing the fluorograms appears to be to mount the individual films in 2 by 2 inch (5 by 5 cm.) slides, with a paper mask on which may be written any information desired.

Potter<sup>9</sup> gave the details of experimental work which was commenced in the United States in 1934, which included the production of fluorograms of 35 mm. dimension, and resulted in making these on 4 by 5 inch (10 by 13 cm.) film. It was his opinion that miniature films of the thorax, to answer well the requirements for case findings, should not be less than 3 or 4 inches (7.6 or 10 cm.) in diameter. Having demonstrated the accuracy of the miniature film in chest surveys by comparisons of these with films of standard size, made at a distance of 6 feet (183 cm.), in one-twentieth second on patients of the Chicago Municipal Tuberculosis Sanatorium, he hoped that some dependable survey group could be induced to undertake a similar demonstration in a true spirit of scientific curiosity and make an authoritative report of the results. His patients were chosen to represent various pathologic types and included men and women of considerable adiposity as well as thin adults and children.

Should the miniature method prove acceptable to men now actively making tuberculosis surveys, Potter felt that it would speed up their work enormously. It might aid materially in clearing up some of the general and some of the special questions foremost in their minds. Among the general questions was the contention of Madsen, of Denmark, that more severe tuberculosis develops among patients who are tuberculin-negative than among those who give a positive test. If this were true, it would make our present inferences from skin tests look rather absurd. As an example of a special question one might mention the finding, either by a sampling process or by wholesale examination, of those parts in any given city in which tuberculosis is most prevalent. The answer to such questions might be obtained soon by a "flexible and economical x-ray method." The outstanding economy derived by use of this miniature method was a reduction of material expense. In cases in which miniatures could be used, the saving was the difference between \$650 a thousand and \$50 a thousand examinations. Having screened out the case showing pathologic interest, the cost of working it up with standard films, made to afford stereoscopic visualization and study, would be the same as it is at present. Secondary economies

in the making and processing of the fluorograms, in facility of filing, and in the decrease of space for film storage are obvious.

Experiments are still being carried out which bid fair to increase the speed and efficiency of screen, lens and film so that a lower milliamperage may be used.

In the discussion which followed his address, Potter stated that routine reading of the miniature films is a simpler procedure than that of full-sized films. The smaller films could be handled with ease because of their size, and the small illuminating box required had a less tiring effect on the eyes, if they were sensitive to light. A new portable apparatus of high capacity for the making of fluorograms was being developed.

While no reference was found to it in a cursory review of the literature, it is common knowledge that work is being done on the development of apparatus which will provide a means of making these fluorograms on film of 35 mm. dimension in sets that will allow for projection and viewing with the aid of polarized glass spectacles; the results will be the equivalent of stereoscopic visualization.

Fluorography, in the experience of Hirsch, is applicable to the study of the skeleton, delineating gross bone changes and deformities. For some years, he stated that he has made studies of the relationship of habitus to visceral morphology, using films of 20 by 36 inch (51 by 91 cm.) dimension, but the high cost of the roentgenograms has impeded this work. By fluorography, however, it will now become possible to make such examinations of large groups at a very low cost.

The practical utility of fluorography has been demonstrated only in a limited field to date; its application has been confined largely to studies of the thoracic cage and its contents in routine or group examinations made as a part of campaigns against tuberculosis; in one instance it had a connection with an industrial survey for evidences of silicosis and other types of pulmonary lesions classified as occupational hazards.

Hirsch stated that fluorography clearly delineates the position and shape of the heart and, if suitable correction factors are used, the diameters of the heart shadows may be determined according to the methods used in teleroentgenography. The Symposium on Heart Disease at the meeting of the American Roentgen Ray Society in September, 1938, dealt largely with the relation of roentgenoscopy and roentgenography to the making of the diagnosis in this type of lesion. Sosman<sup>12</sup> summarized this with the statement that roentgenologists who do not work with physicians well trained in cardiology can contribute more toward the establishment of the diagnosis of heart disease than those whose patients have been accurately and carefully studied by a first class cardiologist. The attitude of the roentgenologist, however, should be coöperative, remembering that the roentgenologic is only one of a number of methods of physical examination. "The roentgenologic method of examination," he stated, "is most valuable when the physician is trying to decide whether or not heart disease is present." It is a well-known fact that valvular disease of the heart sooner or later results in dilatation or hypertrophy of one or more chambers. From the enlargement of a certain chamber and the resultant change in the contour of the heart one can deduce which valves are at fault."

Hodges<sup>5</sup> found that the voluminous literature in the field of cardiac

roentgenology was devoted to a considerable extent to the subject of cardiac measurement. Although the normal position of the heart during life cannot be reliably described with anatomic accuracy, because of its normal mobility, certain relationships are relatively constant. Because distortion is inevitable when an object is projected in a beam of divergent rays, it is important to take steps to minimize this distortion in preparing silhouettes intended for use in estimating size. Hodges described in detail the positions of the patient in relation to the target-film axis best suited to the delineation and illustrated the normal appearance of the heart and great vessels in these various positions and appended standards of normal measurements. Robb and Steinberg<sup>10</sup> described what they had found to be a practical method for visualizing the four chambers of the heart and the thoracic blood-vessels of human beings. Their method consisted of: 1, the rapid peripheral intravenous injection of enough radiopaque solution (concentrated diodrast—70%) into the blood stream to make the interior of the heart opaque to Roentgen rays during the first circulation and 2, the making of roentgenograms of the cardiovascular structures at the moment of their opacification. They illustrated the changes noted in rheumatic heart disease, syphilitic cardiovascular disease, aortic aneurysms, hypertensive cardiac disease, and arteriosclerotic and cardiovascular disease. Freedman<sup>2</sup> found the best differential diagnostic sign between a decompensated heart and pericardial effusion was based on the change of cardiac configuration during changes in the position of the patient as described by Holmes. The most reliable method was the daily Roentgen examination of the heart and the finding of considerable change in its size within short periods of time. Cardiac compression attributable to pericardial scar formation has some features that may be recognized roentgenographically; the degree of fixation resulting may be determined with the aid of expiratory and inspiratory postero-anterior roentgenograms taken with the patient lying on either side and with lateral views taken during inspiration and expiration. The most conclusive sign of cardiac compression, calcification of the pericardium, when present, is visible in roentgenographic examination. Sosman described the roentgenoscopic appearance of calcification in the valves and stated that the demonstration of these lesions added considerably to the accuracy in both structural and etiologic diagnoses. Levene<sup>7</sup> remarked on the changes in cardiac size, contour and activity, occurring frequently in systemic disease. He discussed the roentgenologic features of non-valvular disease of the heart. In myocardial insufficiency, hypertension and hypertension of lesser circulation he found that distinctive roentgenologic appearances were produced. Careful roentgenologic study, therefore, was well suited to the identification and appraisal of disturbed cardiac dynamics. Its importance was further increased by its ability to depict the relationship of the greater and lesser circulation in the individual case. It offered confirmatory evidence of a diagnosis established by other clinical methods and frequently assisted in the differentiation of the causes of cardiac enlargement and decompensation. When signs of heart disease are found before the age of twenty, the diagnosis usually lies between a rheumatic and a congenital lesion. Prior to the advent of cardiouroentgenology a good many cases were not diagnosed or passed through life classified as heart disease of rheu-

matic etiology. In Roesler's<sup>11</sup> material positive roentgenologic findings were present in 85 % of all cases; these findings were of definite diagnostic value in 51 %. Abnormalities in the pulmonic area were approximately three times more frequent than in the aortic area. Telcroentgenoscopy was the ideal method of examining the aorta and pulmonary artery, but in the opinion of Sussman<sup>13</sup> ordinary roentgenoscopy in experienced hands was quite satisfactory. Modern practice requires that the investigation should be made in at least the postero-anterior, right and left oblique and lateral positions. Mensuration is important but must be practiced only under conditions in which the projection error is minimal, that is, either from orthodiagraphic tracings or from telcroentgenologic studies. Roentgenography must be supplemented by roentgenoscopy for the study of pulsation, mobility, density and course.

**Economic Aspect.** The most universal acknowledgment of the accuracy of the roentgenographic method of diagnosis over all other known methods by the recognized authorities concerned with diseases involving the contents of the thoracic cavity has impressed so many clinicians that today the greater number of them regard roentgenographic examination as an integral part of every routine examination. Continued experience with this method of examination has confirmed this opinion and it also has demonstrated the need for multiple roentgenograms made with the patient in various angles in relation to the axis of the light beam, if the accuracy of the method is to be maintained. This tendency toward multiple roentgenograms was noted throughout the various addresses given at the Symposium on Heart Disease as necessary to successful study and accurate diagnosis. This multiplication of roentgenograms has materially increased the cost of the individual examination and probably is a vital factor in the increase of the cost of medical care which is the subject of much thought and discussion at present.

Potter has exemplified this cost factor in group survey work in connection with the prevention and cure of pulmonary tuberculosis with his quotation of Plunkett that the cost for finding one case of pulmonary tuberculosis in the age group from birth to 14 years was over \$4,000. He asserted that in cases in which miniature films (4 by 5 inches) could be used this cost could be lowered to at least one-thirteenth of the cost of the older methods. De Abreu<sup>14</sup> found the use of 35 mm. film in a similar line of endeavor lowered the cost to approximately 12.4 % of that of using 30 by 40 cm. (12 by 16 inch) roentgenograms.

In using fluorography for the examination of the thorax of recruits in military mobilization Holfelder and Berner made 300 to 350 examinations per hour and the resulting films were satisfactory for diagnostic purposes. They felt that as many as 500 films could be examined in an hour and an accurate diagnosis could be made from the miniature films (24 sq. mm.) in all cases. They studied 10,598 films and the findings were normal in 93.1 %; pulmonary tuberculosis was detected in 0.87 % and cardiac abnormalities, in 0.05 %.

**Comment.** Hospitals and other organized medical units were created to provide services which were beyond the means and the ability of the individual practitioner to render at a cost within the means of the majority of persons.

In these organizations it was found that a liberal use of laboratory services, even to the point of routine examination of every patient admitted, materially reduced the time the patient spent in the hospital and also resulted in a significant reduction of the time and effort required by the individual patient from members of the professional staff.

Because it replaced conjecture with factual graphic evidence in all cases in which it was applicable, roentgenologic investigation became an indispensable feature of every such organization.

The experience of the astute and open-minded clinician was that in the examination of the thorax the roentgenologic method attained a degree of accuracy unattainable by any other method. The same was true of examination of the alimentary canal and of the bones and joints. There has been a growing tendency to request a primary roentgenologic examination with subsequent correlation of the factual data of this with that of all other examinations.

To maintain and increase the efficiency of the roentgenologic method it was found necessary to increase the number of films used in the individual examination. For example, in the symposium on heart disease previously mentioned the necessity of multiple roentgenograms with the patient in various positions in relation to the target-film axis was stressed. Roentgenograms were made to check roentgenoscopic observations and to serve as permanent records of these examinations.

While roentgenologic examination has had many advantages, no doubt, it has at the same time been a factor in the increase in the cost of medical care. As in all other lines of human endeavor, much time and thought is being spent on ways and means to lessen this financial burden without prejudice to the efficiency of the service rendered. It may be that in this seed of thought, planted in 1911 by the then acknowledged dean of roentgenologists, Caldwell, and revived in a true spirit of utilitarianism by Potter, whose opinion is highly regarded professionally, rests the solution of the problem as far as medical practice is concerned. One is encouraged in this thought by the enthusiasm concerning the possibilities of the practical application of fluorography shown by still another roentgenologist of erudition and long experience, Hirsch, in his comprehensive presentation of the facts known to date concerning this new procedure.

Because of its dual interest to those working in the field of preventive medicine and those engaged in the practice of medicine this subject seems to deserve the serious consideration of the medical profession as a whole and the earnest coöperation of all who are in a position to assist in its development.

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## PHYSIOLOGY.

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF MARCH 19, 1940

**The Effect of Asphyxiation by CO<sub>2</sub> on the Gas Content of the Swimbladder of Some Marine Fish.** VIRGINIA SAFFORD (Biological Laboratory, Swarthmore, Pa). It is generally agreed that the main function of the swimbladder of fish is to maintain the buoyancy of the fish at different depths. This hydrostatic activity involves gas exchange. The following experiments showed gas exchange in physoclistous marine fish where no apparent hydrostatic activity was involved, but gases passed by diffusion across the gills from the sea water to the blood, were transported by the blood and diffused out at the swimbladder. Likewise oxygen passed out of the swimbladder during the course of the experiments and so became available for respiration. The amount of oxygen which was absorbed was shown to be limited in proportion to the tension of CO<sub>2</sub> which had been transported from the water to the swimbladder.

The scup, sea robin, cunner, tautog, killifish and toadfish (all marine physoclisti) were bottled by the method of Fry and Black (*Am. J. Physiol.*, 126, 497, 1939) in sea water with various tensions of CO<sub>2</sub>. The water was analyzed for CO<sub>2</sub> and O<sub>2</sub> after the death of the fish, and the results established a characteristic curve for each species, *i. e.*, the ability to use the oxygen in the water decreases with increase in tension of CO<sub>2</sub>. The sea robin is asphyxiated by 40-60 mm. CO<sub>2</sub>, the scup by 60-80, the cunner by 100-140, the tautog by 140-160, the killifish by 200-240 and the toadfish by 250-280 mm. CO<sub>2</sub>.

After asphyxiation of the fish the CO<sub>2</sub> and O<sub>2</sub> content of the swimbladder gas were determined as well as the gas content of the water. The analyses showed that CO<sub>2</sub> is readily transported from the water across the gills to the blood and given off into the swimbladder, but that the amount of CO<sub>2</sub> in the swimbladder reaches a maximum pressure approximating the tension of CO<sub>2</sub> in the water to which the fish is sensitive. The oxygen is absorbed from the swimbladder in considerable quantities during the course of asphyxiation in the presence of little or no CO<sub>2</sub>. When CO<sub>2</sub> is added to the water and transported to the swimbladder, less oxygen is absorbed from the swimbladder. It appears, therefore, that the presence of CO<sub>2</sub> which limits utilization of oxygen at the gills is effective in the same way at the swimbladder membrane.

**6(α)-Hydroxy-Progesterone.** MAXIMILIAN EHRENSTEIN and THELMA O. STEVENS (George S. Cox Medical Research Institute University of Pennsylvania). The preparation of progesterones and desoxy-corticosterones which are hydroxylated at various carbon atoms of the sterol nucleus appears desirable in order to investigate the chemical specificity of "corpus luteum hormone" and "cortin" action. The acetate of the 6(α)-hydroxy-progesterone was obtained by means of the following

procedure: 5-pregnan-20-on-3-ol yielded with hydrogen peroxide pregnan-20-on-3 ( $\beta$ ), 5, 6 (trans)-triol; m.p. 256-258°. (See also: M. Ehrenstein, *J. Organic. Chem.*, 4, 506, 1939). Acetylation of the latter furnished the 3, 6-diacetate; m.p. 215.5-216.5°. With special precautions, a partial saponification was performed whereby the hydroxyl group at carbon atom 3 was set free. M.p. of the 6-mono-acetate: 222-226°. Oxidation of the latter compound with chromium trioxide furnished pregnane-3, 20-dione-5, 6(trans)-diol 6-mono-acetate; m.p. 215-217.5°. This compound was dehydrated by means of dry hydrochloric acid in a solution of chloroform. Thereby 4-pregnane-3, 20-dion-6( $\alpha$ )-ol acetate [6( $\alpha$ )-hydroxy-progesterone acetate] was obtained; m.p. 145-146°. Saponification furnished the free 6( $\alpha$ )-hydroxy-progesterone. It ought to be stated that this new substance is an isomer of desoxy-corticosterone. It differs from the latter insofar as the hydroxyl group is not attached to the side chain but to carbon atom 6 of the sterol nucleus.

The substance possesses a marked progestational activity; 5 mg. gave a strong response in the Corner-Allen test (tested by Dr. A. W. Makepeace). Since this dosage was arbitrarily selected, it is not known whether a smaller amount would produce the same effect. According to the literature, progesterone gives a positive Corner-Allen reaction when tested with 1 mg. The 6( $\alpha$ )-hydro-progesterone acetate will also be examined for "cortin" activity.

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**The Effect of Diet Upon Liver Composition in the Presence of Common Duct Obstruction.** JULIAN JOHNSON, I. S. RAVDIN, HARRY M. VARS, and HAROLD A. ZINTEL (Harrison Department of Surgical Research). Dogs were given high fat diet for 2 weeks, thereby raising their hepatic fatty acids concentration. They were then subjected to complete cystic and common duct obstruction. Various diets were compared regarding their efficiency in lowering the hepatic fatty acid concentration in the presence of common duct obstruction.

A diet high in protein and carbohydrate with no fat was found to be the most effective in reducing the liver fatty acid concentration and in increasing the liver glycogen in the presence of common duct obstruction. This diet gave approximately the same results as the usual high carbohydrate diet in about one-half the time.

An adequate caloric intake is essential in the preoperative treatment of the biliary patient. If the caloric intake is low it is especially important that the diet contain no fat.

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**Experiments Upon Air-borne Infection.** WILLIAM FIRTH WELLS (Laboratories for the Study of Air-borne Infection, University of Pennsylvania). Evaporation of minute droplets expelled in expiratory processes enables infection to ride these droplet nuclei on air-currents. Quantitative experiments upon animals, inhaling nuclei-infected air, demonstrate the penetration of these nuclei to the depths of the lung with consequent production of disease.

Studies indicate that the transfer of nuclei infection from infector to infectee varies with the conditions of sanitary ventilation. The equilibrium concentration predicted by the ratio of the elimination rate

to the addition rate of test organisms in semi-enclosed spaces corresponds to the concentration of nasopharyngeal organisms determined by sanitary air analysis.

Respiratory infection, manifested by disease, exhibits the same epidemiologic pattern of spread through aggregations sharing common atmospheres as do droplet nuclei and nasopharyngeal organisms. The pattern formed by interlocking aggregations thus conforms to the pattern of epidemic spread of childhood contagions.

Similarity of pattern of spread of latent respiratory infection to clinically manifest contagion has been shown by immunity and sensitivity tests, and by epidemiologic studies of age incidence. Though many factors complicate the clinical pattern of spread of air-borne infection, there is no reason to believe that the epidemic pattern of infection spread differs from the simple basic pattern of spread of clinically manifest contagion.

Aggregation within the same enclosed atmosphere implies the proximity in time and space which dominates the idea of contagion, and is implied by the term "contacts." Air-borne infections thus become contagious infections. This hypothesis of air-borne infection creates a vehicle adequate to convey infection with the velocity and universality characterizing contagion.

Recognition of vehicles of spread of infection leads to methods of disease prevention. Studies on prevention of contagion by the bactericidal irradiation of the air we breathe promise conclusive evidence of the importance of air as a vehicle of contagion.

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ORIGINAL ARTICLES.

THE ANTI-ENZYMATIC NATURE OF SULPHANILAMIDE'S  
BACTERIOSTATIC ACTION.

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Of equal importance almost, with the epoch-making therapeutic accomplishments of sulphanilamide, is a precise knowledge of its *modus operandi*. Indeed, as far as the future of chemotherapy is concerned, such knowledge may come to be regarded as of paramount importance. Previous to the submission of the experimental evidence now to be presented, all of the theories heretofore proposed concerned an ultimate mechanism of action in a rather indirect way only. That is to say, they seemed to indicate that certain of the body's fluids—such as blood serum, spinal fluid and urine<sup>4,15,17a</sup>—either enhanced very materially the action of the drug or *vice versa*, the drug reinforced the naturally rather weak antiseptic action possessed by these fluids to the point of therapeutic effectiveness. This mutual reinforcement, known as potentiation, has also been clearly shown when both sulphanilamide and specific anti-sera are administered to the same case.<sup>1,5,8</sup>

However, such observations left entirely unanswered the question as to which of these effects is the primary one; nor did they afford even a clue in explanation of their antiseptic (bacteriostatic) effect in terms of a measurable interference with one or more specific biochemical functions of the germ in question. This approach

which is anti-enzymatic in nature, is practically speaking, a distinctly new one as far as the history of chemotherapy is concerned, and its outlines will now be briefly formulated.

*Essentials of the New Theory.* One of the requisites of a good bacterial culture medium is that it contain substances that neutralize the waste products formed by the growth of the micro-organism. Thus blood stimulates the growth of hemolytic streptococci and pneumococci, partly because one of its components destroys the hydrogen peroxide normally formed by both of these germs. The substance responsible for this action is the enzyme catalase which converts the growth-checking hydrogen peroxide into water and oxygen. The hydrogen peroxide is therefore not permitted to accumulate to levels which would be toxic for the micro-organism. The opposite effect is obtained, if for any reason catalase fails to function.

A compound possessing the property of inactivating catalase is spoken of as being anti-catalytic. Our experimental evidence indicates that when sulphanilamide undergoes slight oxidation, it becomes by the same token anti-catalytic. When aqueous solutions are exposed for a brief period to ultraviolet light, the anti-catalytic property is enhanced several fold.<sup>13</sup> The experimental evidence also suggests that the oxidative processes going on within the growing germ represent the oxidative equivalent of ultraviolet light. The net result of the anti-catalytic effect is not to kill the germ necessarily, but to reduce its growth rate and render it vulnerable to the immune forces of the blood serum and phagocytic cells, which complete its destruction. Thus a pure chemotherapeutic effect, which initially is bacteriostatic only, may become bactericidal as the result of a secondary coöperation by the host's protective powers.

The question necessarily arises as to how an anti-catalase produced from sulphanilamide is capable of inactivating the enormous amounts of available catalase, for which the blood or medium constitutes a reservoir. It is best answered by reference to Chart 1, which indicates diagrammatically the state of affairs which may be presumed to obtain in the immediate zone about a pneumococcus. Here hydrogen peroxide is being elaborated within the cell and destroyed by the catalase, which diffuses into it from the environment. Sulphanilamide is altered to anti-catalase (AC) by the oxidative processes in the cell and as a result, the anti-catalase is present in the zone about the organism in maximum concentration. This anti-catalase exerts the effect of a barrier, thus explaining the consequent accumulation of hydrogen peroxide in the *same* zone. Thus, it would appear that the catalase reserves, that is, the total amount of catalase present, play little part in the reaction and that their neutralization *in toto* need not be postulated.

*The Experimental Evidence.* In order to demonstrate the validity of our theory it is first necessary to show that hydrogen peroxide

accumulates in the pneumococcus cultures at the same time that their growth is being checked. Such a demonstration has especial significance, in view of the fact that slowed growth on the part of a culture would naturally yield less peroxide, inasmuch as this substance results from the growth activities of the microorganisms. Inasmuch as the studies demonstrating this point have already been published in their technical detail, the latter will not be repeated here. However, the following references are pertinent, Nos. 11, 14 and 19.

With the technique employed, detectable peroxide always appeared between 2 and 3 hours in both sulphanilamide and control cultures. From the third hour, retardation in growth was apparent in the cultures containing sulphanilamide. The amount of peroxide

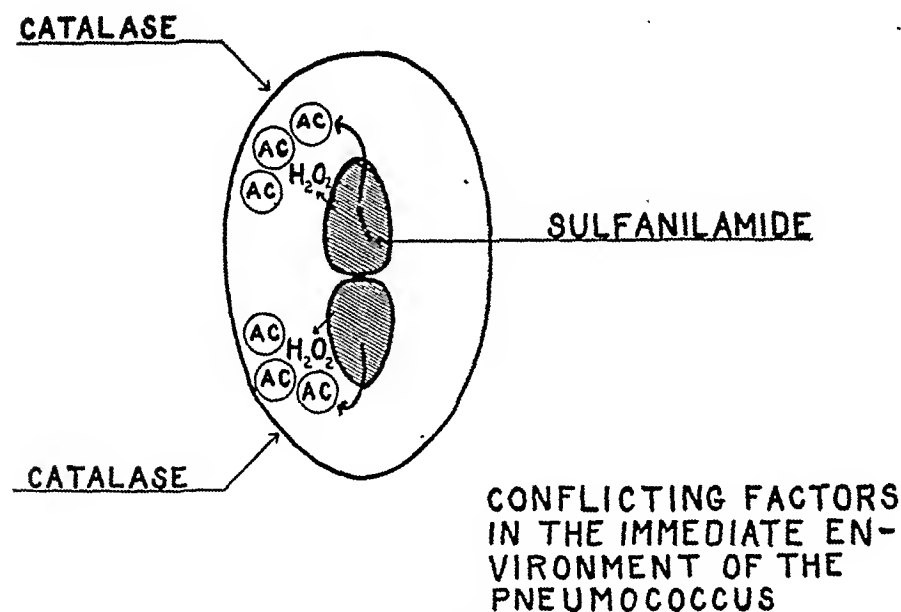


CHART 1.—Showing the oxidation of suphanilamide within the germ to enzyme-poisoning substances (AC), thus permitting accumulation of the toxic hydrogen peroxide.

accumulated in these cultures continued to increase, although the growth, as compared with that of the controls, was becoming increasingly less (Chart 2). Thus the amount of peroxide per unit of bacterial substance became progressively greater in the presence of sulphanilamide. The peroxide concentrations attained at the 5-hour period in the cultures containing sulphanilamide were of the same general magnitude as is required to cause a corresponding inhibition of growth when peroxide was added to a similar culture without sulphanilamide (0.001 to 0.003 %).

A second consideration of paramount importance in connection with hydrogen peroxide as a significant implementing factor in sulphanilamide bacteriostasis, is its dependence on an adequate supply of oxygen. Indeed, it has already been pointed out that the

formation of hydrogen peroxide requires time and oxygen, "points of sufficient importance as possible limiting factors in the application

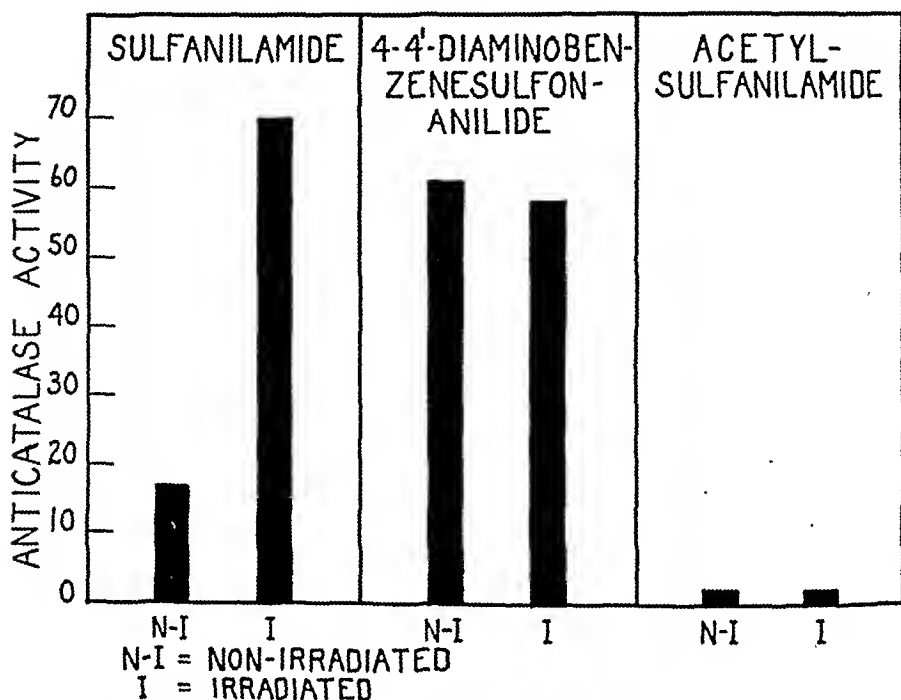


CHART 2.—The anti-enzymatic effect of ultraviolet irradiation on sulphanilamide and related compounds.

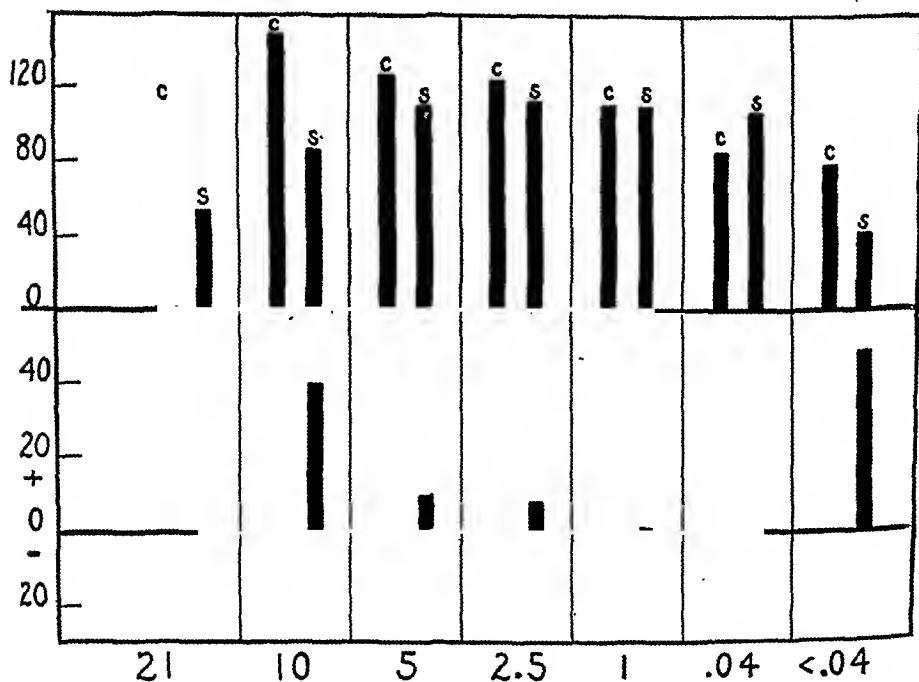


CHART 3.—Necessity for the presence of oxygen for conversion of sulphanilamide to bacteriostatic substances.

of sulphanilamide therapy to occluded and rapidly developing infection to warrant inquiry and test."<sup>10</sup> Therefore, it would be important to show that a progressive decrease in oxygen tension of the cultures is accompanied by a decrease in the bacteriostatic effect caused by sulphanilamide. The dependence of the inhibitory power of sulphanilamide on oxygen has been examined experimentally *in vitro* with reference to the Type I pneumococcus<sup>19b</sup> and the results are herewith summarized (Chart 3).

**Results.** It is clear from the above chart that the average growth inhibition in the presence of air (21% oxygen) is 54%. When a 10% concentration of oxygen is employed, the inhibition is 40%, and the decrease continues until a concentration of 1% oxygen is reached, where the inhibition is essentially zero. No hydrogen peroxide was detected in any cultures at lower oxygen levels. Correspondingly, bacteriostasis almost disappears between the 10 and 5% oxygen levels.

There is, however, an important exception to this rule which requires explanation. When the oxygen concentration reaches the very low level of 0.04%, there is stimulation of growth in the sulphanilamide cultures; but on still further reduction of available oxygen by pyrogallate or hydrosulphite, marked inhibition of growth again appears. This paradoxical situation finds plausible explanation in the peculiar chemical constitution of the sulphanilamide molecule. That is to say, the anti-catalase activity appears to depend primarily upon the activation of the free amino group by oxidative processes, while the sulphonamide group may become reactive under anaërobic conditions. Reference to formulæ of sulphanilamide derivatives below shows that the sulphonamide group is susceptible to reduction\* to sulphides which are rather characteristically toxic. It is possible that the reappearance of bacteriostasis at extremely low levels may be caused by perceptible amounts of these toxic sulphides, which in the infinitesimal amounts produced at slightly higher oxygen levels (0.04%) result only in stimulation of growth.

Although there is a paucity of precise information of sulphanilamide's bacteriostasis under anaërobic conditions, the recent study of Broh-Kahn<sup>2</sup> shows that *B. coli* when respiring under strictly anaërobic conditions is inhibited in the presence of sulphanilamide. This appears to be due to the drug's inactivation of the enzyme, nitratase, thereby preventing the transfer of the oxygen of sodium nitrate to sodium lactate, which is another important component of the special medium employed. Practically, the question of importance that arises is the extent to which such conditions ever prevail in the tissues. The oxygen present in arterial blood, for example, has been stated to be 0.6%.

\* The sulfonamide group is distinguished by being reduced to the thiophenol group with relative ease, as compared to the free sulphonic acid.



Assuming the solubility of oxygen in broth to be essentially the same as in water, and assuming that equilibrium is attained at the higher levels of oxygen concentration, the oxygen present in cultures with atmospheres containing 21%, 10% and 5% oxygen would be 0.5, 0.24 and 0.12% respectively. Thus under normal conditions the amount of oxygen present in plasma is adequate for the support of a high degree of inhibition by sulphanilamide.

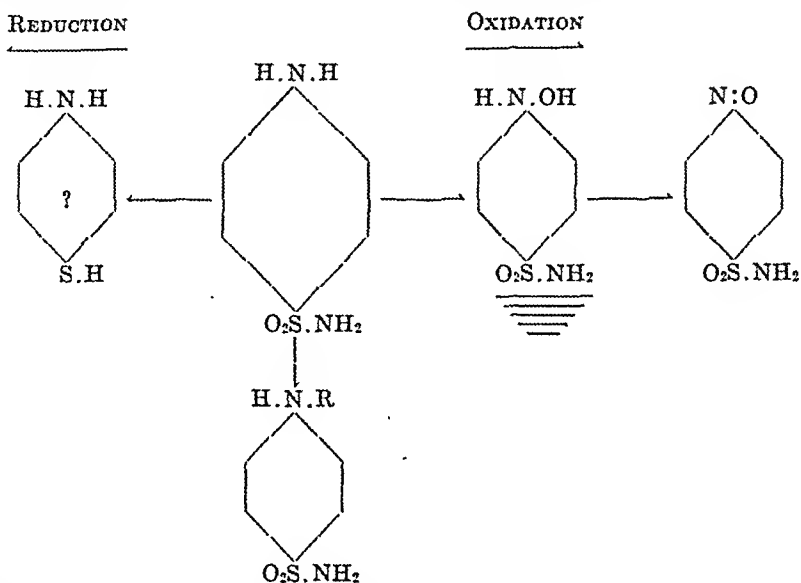


CHART 4.—The rôle of oxidation-reduction in conversion of sulphanilamide to bacteriostatic derivatives.

*The Chemistry of Sulphanilamide Functioning as an Anti-catalase.* The validity of the theory under discussion may be amplified, not to say illuminated, by reference to Chart 4. The rôle of oxidation, reduction, and substitution in the formation of bacteriostatic compounds is represented here. The larger ring shows the structure of sulphanilamide itself, while to the right are shown two steps of oxidation toward the *p*-nitro derivative. To the left is shown the hypothetical thiophenol, referred to above as possibly being responsible for bacteriostasis under anaërobic conditions. Below a typical case of substitution in the *p*-amino group is exemplified by acetyl sulphanilamide.

It is a well-known fact that hydroxylamine is a very potent anti-catalase. It has been pointed out earlier in this paper that oxidation of the type produced by ultraviolet light acting on aqueous solutions endows sulphanilamide with marked anti-catalase properties. It therefore appears reasonable to select the first step of the oxidation, that is, the hydroxylamine derivative, as the seat of this activity.

It is also reasonable to believe that this compound should be as easily produced from sulphanilamide by peroxide-producing pneumococci and streptococci as the result of equivalent processes of

oxidative disintegration. This belief is supported by the experiments illustrated in Chart 2, which shows a rise in the level of hydrogen peroxide even in the face of a diminishing growth rate of the microorganism. It is well known that when sulphanilamide is ingested, a large percentage of it is acetylated by the body and eliminated in the form whose type formula is seen at the bottom of the diagram. It is obvious that acetylation blocks the capacity for oxidation. Moreover, this derivative is found to be quite inactive therapeutically and, according to the oxidative tenets of our theory, we should expect it to be lacking in anti-catalase properties. By test we actually found this to be the case. In other words, lack of anti-catalase activity and therapeutic *inactivity* go hand in hand (Chart 5).

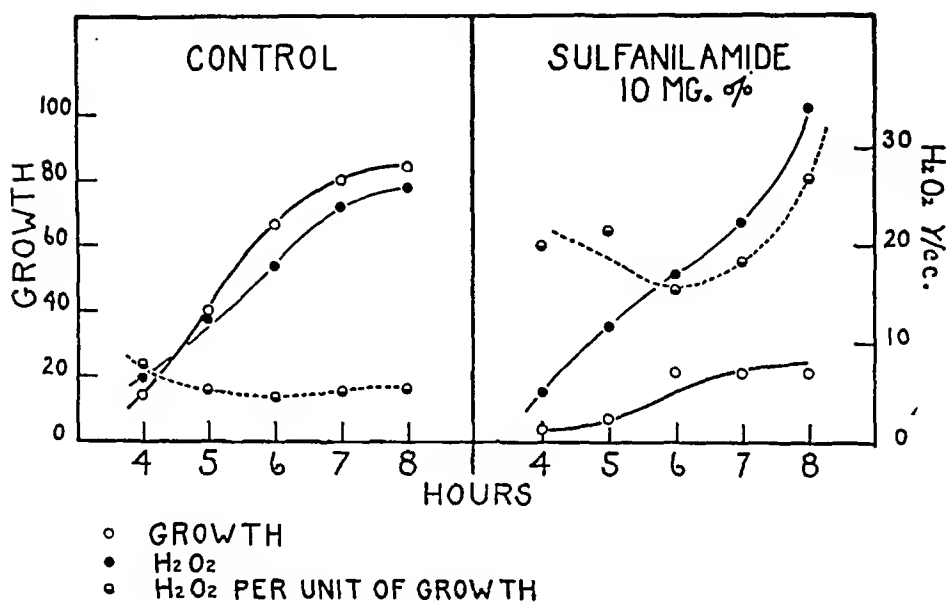


CHART 5.—Accumulation of hydrogen peroxide in sulphanilamide-containing cultures, even in the presence of a diminishing growth-rate.

Recent findings on another class of compounds have shown that the hydroxyl-amino group need not reside in the para position. The sulphonhydroxamides, which may be devoid of any para substituent, but which have a preformed hydroxyl-amino group attached to the sulphur atom, possess definite anti-catalase properties and correspondingly strong bacteriostatic power. However, there is as yet no evidence that the hydroxamide group can be formed from the amide group *in vivo* and hence in the case of sulphanilamide the activity must be referred to the *p*-amino group.

Thus it would appear that the anti-catalase property of the drug is associated with a mild oxidation of the *p*-amino group. When ultraviolet light is used as the oxidizing agent, colored compounds are simultaneously produced. Estimations of the anti-catalase

activity of irradiated and non-irradiated solutions of sulphanilamide showed that a marked increase in this activity appeared simultaneously with the development of such colored oxidation products. However, the anti-catalase derivatives were clearly not identical with the colored products.

Irradiation of 17 compounds related in structure to sulphanilamide showed that color—and therefore anti-catalase activity—was generally produced when the *p*-amino group was free, and the sulphonamide group was free or either partially or wholly replaced by an alkyl group.<sup>13</sup> For example, no color was produced by compounds which have substituents in the *p*-amino groups, and this finding corresponds with what we have observed with sulphanilamide itself, as a result of its acetylation. But the presence of the sulphonamide group may be related to color production indirectly, inasmuch as no color was elicited by irradiation of compounds in which this group was replaced in whole or in part by aryl substituents.

*The Oxidation-reduction Potentials Method and Its Bearing on the Anti-catalase Theory.* By making use of electrical methods it is now possible to measure with a high degree of accuracy the formation in bacterial cultures of oxidizing or reducing substances. The method is of especial value when the amounts of the substance to be detected are minute, and when it is desirable to know the amounts being formed at brief intervals of time. However, the method gives no indication of the chemical identity of the oxidizing or the reducing agents elaborated by the growing cultures. The curve shows an elevated potential in the presence of oxidizing substances, and the opposite when reducing substances are formed.

Thus in cultures where peroxide was accumulating we should anticipate an elevated potential, and a stationary or falling potential if peroxide was being destroyed by catalase as fast as it was formed. In like manner the addition of reducing agents results in a falling potential. From two independent sources<sup>6,20</sup> has come information covering these and related considerations. The subtended table (1) correlates their findings with our own. Although the two experimental approaches are different from the ones employed by us, they are mutually supplementary and should therefore be harmonious.

The elevated potential of the sulphanilamide-containing cultures contrasts with the falling one in normal cultures and is wholly consistent with our findings of increased peroxide production in the presence of sulphanilamide. In correspondence too is the effect of cystein whose anaërobic proclivities within the cultures have the same net result as our rather different method of withholding oxygen from the organism. Likewise, the lowering effect of catalase on the potential which is in contrast with the elevating effect of the anti-catalytic sulphanilamide. Pointing in the same direction is the lowering effect of acetyl-sulphanilamide which, as has been pointed out:

above, has no anti-catalase effect either before or after irradiation with ultraviolet light. The well-known therapeutic effect of sulphapyridine against pneumococcal infections would be anticipated to produce a rising potential as the result of its rôle in effecting an accumulation of hydrogen peroxide, which was confirmed in our tests for it. In fact, it was somewhat more effective than sulphanilamide itself.

*Morphologic Aspects of Sulphanilamide's Action.* In a previous paper<sup>17b</sup> we have taken the position from the experimental data then available that the chain formations characteristically resulting from sulphanilamide's action were not merely "involution forms," which incidentally was the only interpretation given them up to that time. On the contrary, we regarded such pleomorphic structures as distinct phasic entities, although it was admitted that their isolation in culture would constitute the only proof for such a contention.

The experiments substantiating this point of view have recently been published in preliminary form.<sup>16</sup> They show that not only a chained culture phase of the pneumococcus is isolatable, but a bacillary, diphtheroid-like phase, as well as a micrococcus-appearing organism. In short, a dissociative gradient of culture phases has been revealed, which culminates in a loss of the organisms' specific capsule. Moreover, there is a diminishing metabolic gradient, showing suppression of methemoglobin production, inulin fermentation, hydrogen peroxide production, and virulence. All culture phases are reversible to the original mucoid colony of highest virulence. Virtually all stages showing the morphologic gradient are phagocytatable, which lends to the variability changes in the germ a significance of paramount importance, chemotherapeutically speaking.

TABLE 1.—OXIDATION-REDUCTION POTENTIALS IN HEMOLYTIC STREPTOCOCCUS CULTURES CORRELATED WITH  $H_2O_2$  FORMATION AND BACTERIOSTASIS IN PNEUMOCOCCUS CULTURES.

	eH.†	$H_2O_2$ .	Stasis.
Normal culture, no sulphanilamide . . . . .	Falling	—	—
Culture and sulphanilamide . . . . .	Rising	+	++
Culture and sulphanilamide . . . . .	Rising	+	++
Plus cystein . . . . .	Falling	—	—
Culture and sulphanilamide . . . . .	Rising	+	++
Plus catalase . . . . .	Falling	—	—
Culture and acetyl-sulphanilamide* . . . . .	Falling	—	—
Sulphapyridine . . . . .	Rising	+	++

\* This compound, therapeutically inactive, has no anti-catalase either before or after irradiation with ultraviolet.

† Compiled from published reports of Fox, German, and Janeway,<sup>6</sup> and Warren, Street, and Stokinger.<sup>20</sup>

**Discussion.** The most inscrutable aspect of sulphanilamide's behavior lies in its therapeutic efficacy against such diverse species of bacteria as hemolytic streptococci, pneumococci, gonococci, meningococci, and *B. coli*. The fact that all of these organisms produce

hydrogen peroxide and that they are all rather highly sensitive to its toxic effect, offers plausible explanation for the drug's broad therapeutic coverage. Moreover, as McLeod<sup>12</sup> has shown, when the hydrogen peroxide-producing power of the pneumococcus is suppressed, it is no longer vulnerable to the drug; in this case, sulphapyridine.

On the other hand, enzymes other than catalase are affected either directly by the drug or possibly secondarily by the toxic action of accumulated hydrogen peroxide which is known, for example, to inactivate the proteolytic enzyme, papain.<sup>18</sup> We have evidence that peroxydase is adversely affected<sup>17b</sup> and McLeod<sup>12</sup> has shown that certain dehydrogenases are inactivated; while Broh-Kahn<sup>2</sup> has shown that nitratase may also be poisoned. In other words, we are sponsoring an anti-enzymatic conception without, however, limiting the effect to a single enzyme. Moreover, inasmuch as such effects appear to be implemented by oxidation-reduction mechanisms, the conception does not exclude toxin-inactivation as supported by Carpenter.<sup>3</sup> Toxins are notoriously susceptible to oxidation.

The oxidative-enzymatic theories are rather generally supported by clinical evidence. That is to say, virtually all of the infections decisively influenced are of aërobic nature. An exception is the staphylococcus, which, however, is prone to form localized abscesses even when the infection is generalized. The highly reducing nature of these lesions is regarded as preventing the oxidation of sulphanilamide that conditions its anti-enzymatic effect. Whether this explanation is completely adequate will perhaps be apparent when more is known of the action of the sulphathiazoles, which appear especially promising in their effect against this organism.

It is also possible that the protein degradation products present in abscesses may condition the action of the drug in accordance with mechanisms that are not anaërobic. Our previous demonstration of the decisive action of sulphanilamide against *B. coli* in urine, but not in peptone-containing media, was sufficiently clear-cut to leave no doubt of the importance of environmental factors. In fact, they may result in multiplying the effect of the drug many times. This potentiating action, as it is called, is particularly conspicuous when anti-sera are combined with the drug.

The only formidable objection that has been raised to the peroxide-catalase theory is the claim of Fuller and Maxted<sup>7</sup> that Type 3 hemolytic streptococci did not produce hydrogen peroxide. Since the recent demonstration by the Hadleys<sup>9</sup> that these Type 3 strains could readily be dissociated into phases which produced abundant hydrogen peroxide, the objection would seem to have lost most of its force.

**Conclusions.** 1. The free amino group of sulphanilamide when incompletely oxidized becomes poisonous for catalase, as a result

of which the toxic hydrogen peroxide produced by many pathogenic organisms is permitted to accumulate in their cultures.

2. In addition to catalase, other enzymes are adversely affected by the intermediate oxidation products of the sulphonamide compounds. As known so far, they are peroxydase, certain dehydrogenases, and nitrotase. The nutrition of the bacteria is thus seriously affected, and bacteriostasis results.

3. The effect of such bacteriostasis against pneumococci *in vivo* is to bring about their "dissociation" into culture phases, whose principal metabolic functions, including hydrogen peroxide formation and virulence, are so critically suppressed that the organisms fall easy prey to the destructive action of the phagocytes.

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### THE EFFECT OF SULPHANILAMIDE COMPOUNDS ON ENDOCARDITIS.\*

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IN discussing any therapeutic measure which seems to have an effect on certain cases of infectious endocarditis, three outstanding criteria must be satisfied. First, a diagnosis of endocarditis must be established with reasonable certainty; second, we must remember that spontaneous cure of subacute infectious endocarditis occasionally occurs; and third, variation of the virulence of certain infections

\* Presented before the meeting of the American Clinical and Climatological Association, Saranac Lake, New York, October 11, 1939.

from year to year is a well-known fact of epidemiology, a possible factor when considering the experience of Capps.<sup>1</sup>

The diagnostic triad which has been rather generally accepted for the diagnosis of subacute infectious endocarditis or endocarditis lenta is the presence of petechiæ, splenomegalia, and *S. viridans* in the blood stream. The relationship of this triad to give the correct diagnosis of endocarditis lenta is discussed in detail in a recent paper by Middleton and Burke,<sup>7</sup> which is based on the study of 88 cases. These authors found that in their series petechiæ were present in 60%, a palpable spleen was found in 70% of the cases, and streptococci in 70% of the cases. It is noteworthy, however, that 10% of their cases had no blood cultures and 13% were negative from 1 to 6 times.

We have recently made a study of our own cases during the past 6 years, some 15 in number. While this number is not of the magnitude of many studies reported in the literature, yet from our point of view, it has the advantage that every patient was studied personally, examined many times, and followed to necropsy. In our series, petechiæ were present in only 50% of the cases, enlarged spleen in 60%, and positive blood cultures in every case but one. The existence of cases of endocarditis lenta with negative blood cultures is too well established, of course, to be doubted, although the question may still be open as to whether the blood stream itself is actually sterile or whether the culture methods employed may not have been favorable for growth. Our observations indicate that the presence of *S. viridans* in the blood stream in conjunction, of course, with fever and heart murmur is the most important and constant finding in endocarditis lenta. *Streptococcus viridans*, of course, appears from time to time in the blood stream without endocarditis, the result of bacterial invasion from elsewhere. We have seen 2 such cases from subcutaneous infections in which the same organism was recovered from the blood stream. In such patients, however, the positive blood culture lasts only a few days or even hours. In our experience the presence of *S. viridans* in the blood stream in three to five cultures over a period of 1 to 2 weeks is almost convincing proof of the evidence of endocarditis when the other signs are present.

During the past 5 years we have seen an increased interest in the treatment of streptococcic infections which is directly traceable to the work of Domagk, who demonstrated the specific effect of dyes containing sulphanilamide upon streptococci, particularly the beta streptococcus, better known as the hemolytic streptococcus. This work is so familiar that a review of it is quite unnecessary. The effect produced by prontosil or sulphanilamide upon streptococci, and as it was later shown on pneumococci as well, quite naturally suggested its employment in the treatment of subacute infectious endocarditis.

In 1938 Hussey<sup>4</sup> reported—in his own words—a case of “probable bacterial endocarditis, apparently cured with sulfanilamide.” As he himself notes, his diagnosis is open to question since the first two blood cultures were sterile, while the third one showed a hemolytic streptococcus. On the fifth day the patient had an elevation of temperature of 103.6°. Subsequent blood cultures were sterile. The patient received sulphanilamide for 25 days, and was dismissed from the hospital apparently cured 4 weeks after discontinuance of the sulphanilamide therapy. This clinical history obviously bears little resemblance to a typical subacute endocarditis, and the diagnosis of hemolytic streptococcus septicemia would seem more likely. Spink and Crago,<sup>9</sup> reported the beneficial effect of sulphanilamide on 2 out of 12 patients suffering from subacute infectious endocarditis.

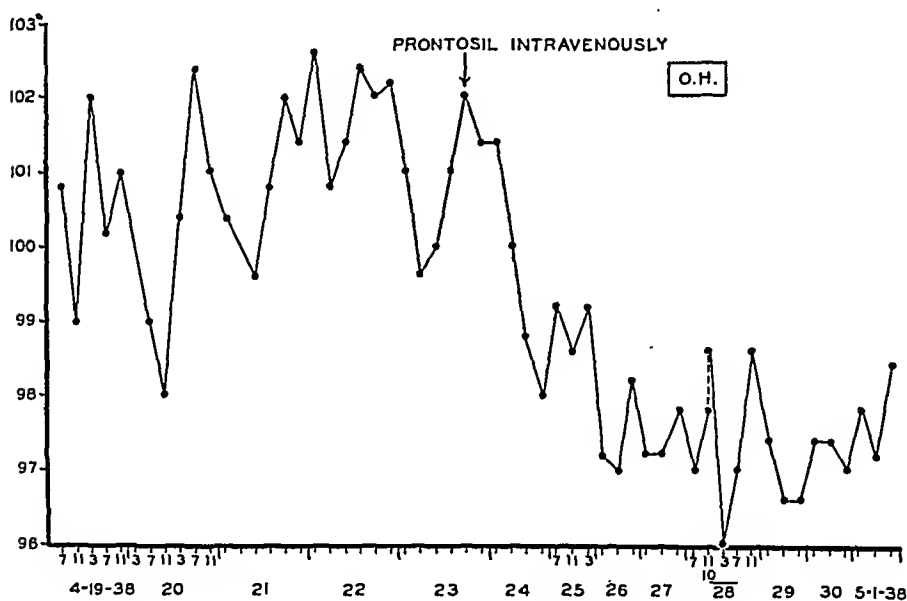


FIG. 1.—Temperature chart, Patient 1.

CASE 1.—On April 13, 1938, a patient was admitted to the University of Kansas Hospitals, and was subsequently diagnosed as subacute infectious endocarditis. This patient had been under observation in the Out-Patient Department for 8 years with the diagnosis of mitral and aortic valvular disease. On several occasions she had been sent home and put to bed for marked cardiac failure.

One month before admission to the hospital, the patient had an abortion which was followed by chilly sensations and some fever. These symptoms apparently lasted only 2 or 3 days, following which she felt perfectly well. One week before admission to the hospital she began to have chills and sweats every afternoon, and apparently some fever.

On admission to the hospital the patient showed an enlargement of the heart. There was a systolic murmur at the apex and a diastolic murmur over the aortic area. The spleen was enlarged and there were a few petechiae over the neck. She showed a moderate secondary anemia.



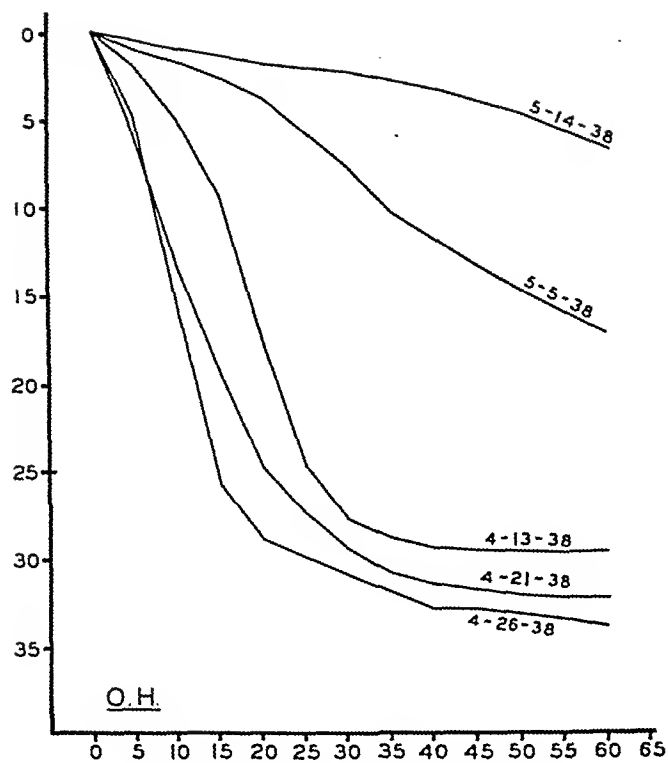


FIG. 2.—Temperature chart, Patient 1.



FIG. 3.—Section of heart valve, Patient 1.

Laboratory examination showed red blood cells 3,940,000, with 78% hemoglobin, leukocytes, 17,500. Blood culture, taken on the day of admission, was positive for *S. viridans*, as were blood cultures on April 14 and 15.

The patient was started on prontosil, 10 cc. intramuscularly twice a day, and 10 grains of sulphanilamide four times a day. Ten days later the prontosil was given intravenously, 10 cc. doses t.i.d. for 2 days and then twice a day until May 13, at which time the treatment of prontosil was discontinued. The patient's temperature did not go above normal on April 26, 13 days after beginning the treatment, and from that time on it remained normal. Blood cultures taken on April 23 and 27 and May 2, 7, 11, 17 and 20 were negative. On May 5 the patient's spleen was no longer palpable. The temperature curve of this patient was very striking (Fig. 1), but even more striking are the sedimentation charts at various periods (Fig. 2).

One month after the patient's temperature had become normal she died from what appeared to be cardiac failure. We were much disappointed, naturally, since we felt we had cured the patient from subacute endocarditis only to have her die of cardiac failure. However, we were comforted by the fact that it would give us the opportunity to study the patient's heart. The study of this heart showed that the patient had both an old aortic and mitral lesion, and in addition to this, a recent endocarditis on both valves, which was in the process of healing, the healing being more marked in the aortic valve (Fig. 3). The cultures taken from the valves were sterile, and microscopic sections gave abundant proof that healing was taking place.

This experience with prontosil filled us, naturally, with a desire to try further the effect of sulphanilamide and allied compounds in the treatment of endocarditis.

The work of Maegraith and Vollum,<sup>5</sup> who found sulphapyridine to have a particularly marked bacteriostatic effect on the *S. viridans*, suggested the employment of this drug. Soon after, we had an opportunity of testing it out on a patient.

CASE 2.—W. G., aged 36, was admitted to the University of Kansas Hospitals March 10, 1939. The patient had had rheumatic fever at the age of 14, which left him with a mitral lesion. The present illness began 1 month before admission to the hospital, at which time the patient observed that he had a daily evening temperature varying from 101° to 102°. Blood cultures at the time of onset showed *S. viridans*. Four other blood cultures were positive. The patient went to bed 3 weeks before admission to this hospital, and during that time received 1350 grains of neoprontosil by mouth, and 190 cc. of neoprontosil intramuscularly. Dr. Corrigan, of Wichita, Kansas, kindly referred him to us for further treatment. At the time of his admission he showed a temperature of 101.6°, a moderate anemia; R.B.C., 3,610,000 with 66% hemoglobin and 14,000 leukocytes. Blood cultures on that day showed *S. viridans*. He was started on sulphapyridine, 1 gm. every 6 hours. His temperature fell to normal in 24 hours (Fig. 4), and he showed no further positive blood cultures, although they were performed regularly three times a week. He was dismissed from the hospital on April 22, 1939, and remains well up to the present time. The patient's sedimentation chart is eloquent witness of improvement in his condition (Fig. 5).

CASE 3.—The next patient who showed a favorable response to therapy was a white woman, aged 40, who was admitted to the University of Kansas Hospitals on August 2, 1939. She had not been in good health for 2 years and for 2 or 3 weeks before admission to the hospital she noticed fever in the evenings accompanied occasionally by a chilly sensation. Physical

examination showed cardiac enlargement, systolic thrill and murmur at the apex. No petechiæ were seen, but the spleen was easily palpable two fingers' breadth below the costal margin. The patient's temperature in

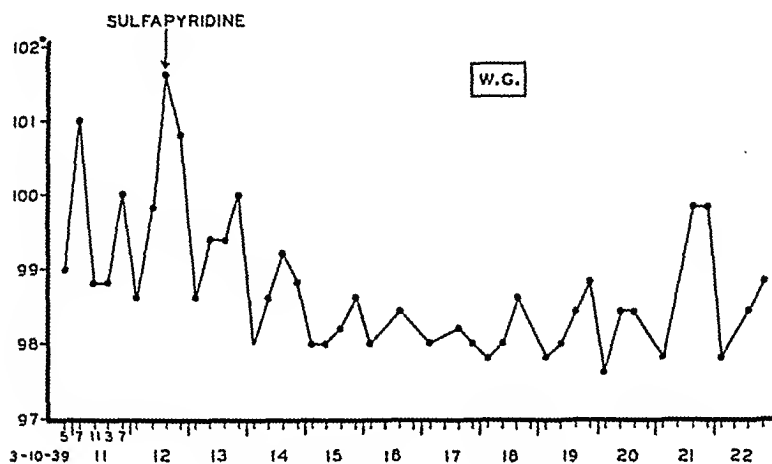


FIG. 4.—Temperature curve, Patient 2.

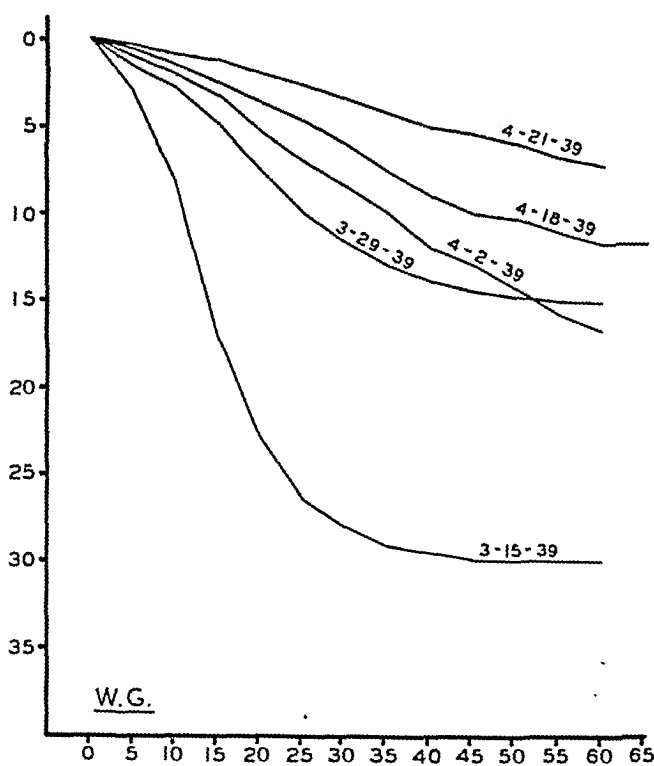


FIG. 5.—Sedimentation rate, Patient 2.

the first few days after admission varied from 99° to 101°. The blood examination showed R.B.C., 4,130,000; W.B.C., 6300; hemoglobin, 59%. Three blood cultures showed the presence of *S. viridans*. Treatment with

sulphapyridine, 6 gm. daily, was commenced on August 12. Blood cultures taken on August 12 and 13 were negative. On August 14, *S. viridans* was present in the blood stream. This was the last positive culture obtained.

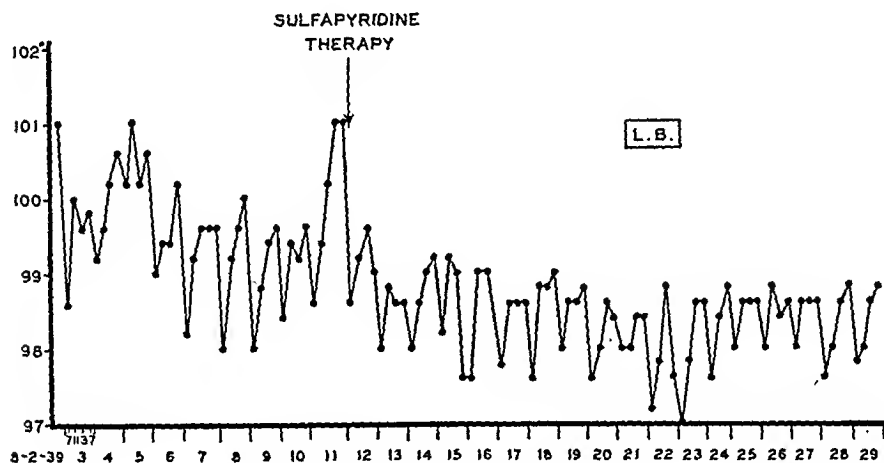


FIG. 6.—Temperature curve, Patient 3.

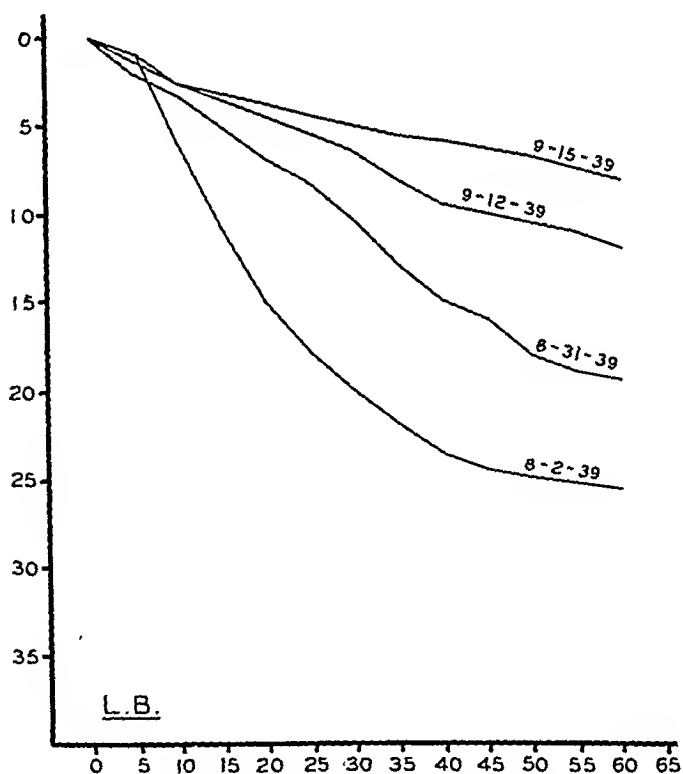


FIG. 7.—Sedimentation rate, Patient 3.

Since this period the patient has had 3 blood cultures weekly; they have all remained sterile. The patient showed marked improvement in her subjective symptoms and the spleen gradually receded in size and at present is

rather palpable on some days while on other days it cannot be felt. The temperature curve and the blood sedimentation rate are shown in Figures 6 and 7.

While this is too short a time to say positively that the patient has recovered from the infection, we are, however, justified in saying that clinically she has shown outstanding improvement and bacteriologically, her blood stream is sterile.

In contrast to these 3 patients who apparently recovered from subacute infectious endocarditis there were 4 patients who died.

CASE 4.—The first patient was a colored man, aged 24, who was in the hospital for 1 month and was treated with prontosil, receiving in all, 15 gm. His blood cultures remained positive and he died 2 weeks after leaving the hospital.

CASE 5.—The second patient was a girl, aged 17, who showed on physical examination the signs of pulmonary stenosis and a patent ductus arteriosus. She was in the hospital from November 25, 1938, to March 9, 1939. She received, during this period, 58 gm. of prontosil and 58 gm. of sulphapyridine and showed 21 positive and 17 negative blood cultures. She died 5 months later. Autopsy showed a patent ductus arteriosus and very profuse vegetations.

CASE 6.—The third patient, a young man, aged 22, who was treated from July 1, 1939, and died on August 14, 1939, received 162 gm. of sulphapyridine and 3 gm. of prontosil. The last 4 blood cultures were negative. Autopsy showed a healing endocarditis, acute and chronic nephritis, and an advanced adhesive pericarditis.

CASE 7.—The fourth patient was a man, aged 27, who was a patient in the hospital from February 27, 1939, until his death on September 16, 1939. He was treated with sulphapyridine and while under treatment showed negative blood cultures from March 20, when treatment began, until nearly 5 months later. Treatment was discontinued on July 28, and the blood cultures became positive on August 10. Treatment at this time was renewed and the blood cultures became negative and remained so until his death 5 weeks later. Autopsy showed an endocarditis and a massive cerebral hemorrhage. Although this patient showed negative blood cultures for 6 months and occasional afebrile periods, his sedimentation rate remained unchanged throughout—the picture of an acute infection.

Our experience of the past year shows then that we have had 7 cases of endocarditis which have been treated with sulphanilamide or sulphanilamide compounds with 3 apparent recoveries.

The question as to whether these recoveries were due to the specific therapy cannot, perhaps, be positively answered at this time. Further experience may be necessary. Such a conclusion, however, would seem to be tentatively justified.

As mentioned above, we saw no recoveries whatever in our last 15 consecutive cases, whereas we have seen a number since with sulphanilamide compounds. Ellis<sup>2</sup> noted that in 2 patients with subacute bacterial endocarditis, treated with sulphanilamide, that the drug apparently had a marked effect on the temperature and improved the clinical condition of the patient although the later outcome was not stated. Ravina describes a patient in whom the temperature fell, and the patient was clinically improved by the

use of sulphapyridine. Whitby<sup>10</sup> has described the use of sulphapyridine in 3 cases of subacute bacterial endocarditis with improvement in general health and comfort, and with marked falling in temperature. The effect upon the temperature may not, however, be specific, since there is evidence that this drug has temperature-lowering effects. We have, however, also noticed striking improvement in the patient's clinical condition, and even in the patients who did not recover, administration of this drug was followed, usually, by an alteration in the blood cultures. Negative blood cultures became more frequent; the number of organisms seemed to be definitely reduced, and certain changes in the morphology of the cocci appeared.

The response to the drug varied in different patients in this series. The first patient who recovered from the endocarditis received only 15 gm. of prontosil and 5 gm. of sulphanilamide in the course of a month. The second patient, who showed no response whatever received 25 gm. of prontosil in 1 month. The third patient, who also showed no improvement whatever, received a total of 50 gm. of prontosil and 95 gm. of sulphapyridine.

The next patient who recovered received 144 gm. of sulphapyridine. The dosage was 4 gm. a day for 36 days. Fortunately, this patient could take the drug without vomiting or nausea. Later this patient's blood was examined for the sulphapyridine content on different days and at different hours of the day—nine determinations in all being made. The sulphapyridine content of the blood never fell below 4 mg. per 100 cc. and was usually from 4.5 to 4.95. The second patient on whom sulphapyridine was used and in whom failure was recorded, showed on one occasion the sulphapyridine at 5.6, but an average that was 3 mg. or less.

The last patient who apparently recovered, took sulphapyridine by mouth with little or no discomfort. She has received 6 gm. per day for 43 days. The blood sulphapyridine content has varied from 1.58 mg. to 8 mg. per 100 cc. After the first 3 days it was constantly above 3 mg. per 100 cc. She has received 258 gm. of sulphapyridine in all, with no bad effects. The blood count improved from 4,130,000 on August 3, 1939, to 4,590,000 on September 20, 1939. The hemoglobin on August 3, 1939, was 59%, and on September 20, it was 83%. The differential count remained normal.

**Conclusions.** Our series of cases, while extremely small, shows a much higher percentage of recovery than reported by any of the other authors except Oille, Graham and Detweiler.<sup>8</sup> The very prompt fall of temperature, appearance of negative blood cultures, disappearance of the enlarged spleen, and markedly improved well-being of the patient, seen after the therapy was instituted, suggests very strongly that we are dealing with a specific effect. I realize, however, that endocarditis lenta, in many instances, is essentially a chronic disease, lasting for months and sometimes years. For this

reason, time will probably speak the decisive word. Meanwhile, we are, however, safe in drawing the following conclusions:

1. Patients with endocarditis lenta, treated with prontosil and sulphapyridine, in some instances show a fall of temperature to normal, the disappearance of the organisms in the blood stream.

2. It is possible that in some cases where the vegetations were small, healing may follow. In other cases where the vegetations were more extensive the organisms will probably live for a long time embedded at the base of the vegetations although the blood stream remains sterile.

3. The blood sedimentation rate has been of great value in determining the activity of endocarditis. In the cases which apparently recovered, the blood sedimentation rate has become normal. In certain other patients, even though the temperature had fallen to normal and the blood stream remained sterile, the sedimentation rate was that of an acute infection and made us very suspicious that the processes remained active, a suspicion confirmed by the subsequent course of events. In 2 such patients the cessation of sulphapyridine resulted in the organisms reappearing in the blood culture.

Addendum—Cases 2 and 3 are clinically well on March, 1, 1940.

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### SICKLE-CELL ANEMIA IN A WHITE FAMILY.

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FOLLOWING the first description of sickle-cell anemia by Herrick<sup>14</sup> in 1910, it was thought for a number of years that this disease was confined exclusively to people of the Negro race. The occurrence of the disease in white persons, however, was reported by Cooley

and Lee,<sup>8a</sup> Pincus and Rosenfeld,<sup>16</sup> Clarke,<sup>6</sup> Cooke and Mack,<sup>7</sup> Haden,<sup>12</sup> and Weiner.<sup>20</sup> These cases, 11 in all, constitute authentic, unchallenged instances of this interesting disease. The majority of the cases occurred in persons from Mediterranean countries, especially Italians. Although additional cases have been reported, they have been questioned for several reasons because of failure to show sickling with microphotographs, mistaken elliptical red cells for sickle cells and because of the great likelihood of the admixture of negroid blood in geographical locations, where inbreeding is obviously quite common.<sup>2,5,15,18</sup> Excellent contributions dealing with the various aspects of the disease have been ably described by many authors.<sup>1,3,4,8a,9a,b,11,13,17,19,21</sup>

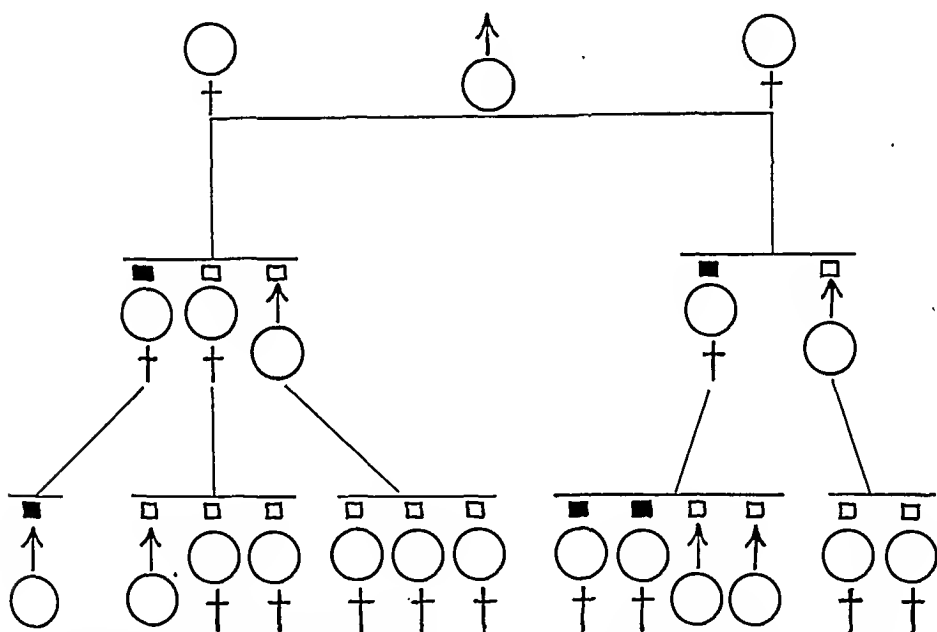


CHART 1.—Black rectangles indicate those who showed sickling of the erythrocytes. To the right the mother and the two daughters; to the left, the aunt and her son.

This communication is concerned with a report of the study of 23 members of a white Italian family of Sicilian birth or extraction, 5 of whom showed sickling of the red blood cells (Chart 1). The ancestors of this family were born and lived in Naro, Sicily, the parents of the persons whose cases are reported immigrated to the United States 32 years ago.

**Case Abstracts.** CASE 1. Lena A., a white female, born in the United States, aged 22, entered the hospital on March 17, 1939. Present illness began 2 weeks before admission, when she suffered with weakness, malaise, epigastric distress followed by abdominal pain radiating to the back, pains in the extremities with localized areas of exquisite tenderness and swellings which were migratory in character, palpitation, dyspnea, slight dysmenorrhea, nocturia three or four times and loss of 8 pounds in



weight since onset of illness. She noticed that the sclerae were yellow, the urine dark red and stools light colored. An identical episode occurred at the age of 9 and recurred approximately every 6 months. The icterus, the pain in the abdomen and the extremities would subside; except for occasional weakness and pains in the limbs she remained fairly well for a period of 3 years preceeding the onset of the present attack.

*Past History.* Varicella and two attacks of pleurisy in the left chest, tonsillectomy 2 years ago.

*Family History.* Parents were born in Italy. Father died of heart disease at the age of 57. Mother, one sister and two brothers are alive and well.

*Physical Examination.* Patient is fairly well nourished. She appears acutely ill: pallor, weakness and general malaise, temperature 101°, pulse 90, respiration 25. The features are not coarse, hair is abundant, straight, brown in color. Sclerae are subicteric. There is no adenopathy, no thyroid enlargement. Chest: small area of tenderness over left anterior chest in the first and second interspaces, no redness or swelling. Lungs: are negative. Heart is slightly enlarged, systolic thrill felt over apex and a systolic murmur at the apex not transmitted. Blood pressure: 104 mm. Hg. systolic, 68 diastolic. The liver percusses three fingers below costal margin. Right kidney is palpable and tender. Positive right Murphy sign. Spleen is not palpable. Extremities: right arm is swollen and exquisitely tender on the inner aspect, no induration, redness nor heat. Right leg, anterior middle one-third is bluish-red and very tender; left leg shows slight pretibial tenderness, no swelling nor discoloration. Skin is free from eruptions or ulcerations. Neurological examination is negative.

*Laboratory Data.* Blood count on admission: Hemoglobin, 62%, red blood cells, 4,700,000; white blood cells, 31,000; platelets, 225,000, color index, 0.66. Differential count: neutrophils, 84%, lymphocytes, 11%, monocytes, 4%, eosinophils, 1%. Erythrocytes showed marked anisocytosis, macrocytosis and microcytosis, polychromatophilia, hypochromia, normoblasts, macroblasts, coarse basophilic stippling and reticulocytosis (see also Table 1). Icterus index ranged between 12 to 4. Fragility of red cells to hypotonic saline began at 0.34% and was not complete at 0.28%. Van den Bergh was positive, delayed, direct. Sedimentation rate 18 mm. in one-half hour and 26 mm. in 1 hour. Bleeding time, coagulation time Rumpel-Leede and clot retraction were all normal, blood Wassermann was negative. Blood proteins: serum albumen, 3.63; globulin, 2.26. Blood chemical findings in mg. per 100 cc.: glucose, 101; NPN, 33; creatine, 1.7; cholesterol, 160. The CO<sub>2</sub> combining power was 55 vols. %. No auto-agglutination present. Urine: Sp. gr., 1.012; albumin trace, moderate number of hyaline casts, rare erythrocytes and leukocytes, bile negative, urobilin present in the 1 to 10 dilution, ascorbic acid, 0.8 mg. per 100 cc. urine, occasional hemosiderin crystal, no hemoglobin. Basal metabolism -5%. Electrocardiogram normal. Roentgen ray studies: liver enlarged and ptosis of right kidney; no biliary calculi; chest, skull and long bones are negative.

On two occasions wet preparations were studied for sickling with negative results. On April 16, 1939, 4 weeks after admission, one of us repeated the test and definite 100% sickling was observed within 24 hours (Fig. 1). This was repeated several times with similar results. The stained blood smears showed very few sickle-cells. Sternal marrow puncture: presents a picture of hyperplastic normoblastic marrow.

*Course.* With bed rest and symptomatic treatment 3 days after admission the fever, abdominal pain and pain in the extremities subsided. The appetite improved but weakness continued. On March 31st, 14 days after admission, patient complained of pain in left anterior chest over the first

and second ribs, 1 inch from the sternum. Two tender, firm, nodular subcutaneous swellings appeared which subsided in 48 hours. She was out of bed and gained weight and was free from symptoms. She was discharged on April 26, 1939 (40 days after admission). She remained well until July 21, 1939, when she complained of pain, swelling of the left arm; this was quite tender over the outer aspect and subsided within 3 days.

TABLE 1.—BLOOD FINDINGS IN CASE 1.

Date.	Hemoglobin.	Red blood cells.	White blood cells.	Neutrophils.	Stab cells.	Segmented cells.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Reti- culocytes in %.	Nucleated red blood cells.	Morphology.
3/18	62	4.7	31.0	84			11	4	1		4	2	Aniso-, macro-, microcytosis, polychromasia, hypochromia.
3/22	63	3.6	26.4	66	3	63	25	4	3	2		7	Hypochromia, marked basophilic stippling.
3/27	56	3.3	25.9	65	5	60	27	5	3			13	As above.
4/4	62	4.1	17.8	72	5	67	14	11	3			6	As above.
4/5	60	4.7	27.2	70	7	63	12	12	5	1		18	Marked aniso-, macrocytosis.
4/6	65	4.9	16.9	71	5	66	25	4				11	As above.
4/11				59	1	58	32	6	2	1	4	11	Hypochromia, aniso-, poikilo-, macrocytosis, stippling.
4/13				60	2	58	27	9	4		4	14	Hypochromia, anisocytosis, few sickle-cells seen.
4/15				60	2	58	30	8	2			13	Anisocytosis, hypochromia, W. P. 100% sickling.
4/17	62	5.1	18.9	65	17	48	25	6	3	1	3	8	Many sickle-cells, anisocytosis, W. P. 100% positive.
4/19				59		59	25	9	6	1		22	As above.
4/24	62	4.3	18.7	63	9	54	28	7	2			21	Anisocytosis, many sickle-cells.
7/21	62	4.5	26.9	70	3	67	16	13	1		5	31	Hypochromia, aniso-, poikilocytosis, polychromasia, stippling, Howell-Jolly body, W. P. 100%.

W. P. = wet preparation for sickling.

It is obvious from the clinical course and hematological findings that this patient presents the typical picture of sickle-cell anemia in its acute phase.

Accordingly, all the available relatives of the patient were requested for examination. Twenty-two other members of the family were studied for the sickle-cell trait, 4 of whom showed this phenomenon with 100% sickling in 24 hours. These included the patient's mother, and a younger sister 9 years old, an aunt 26 years old and her son 6 years of age. Because of typical features in the case of the child of 9, we wish to report her as the second case of sickle-cell anemia in this series.

CASE 2.—Laura A., aged 9, has had measles, pertussis, otherwise enjoyed good health. Examination reveals a fairly well nourished Italian child

with features similar to those of her sister. The positive findings consist of slight pallor, sub-icteric tinge to the sclerae, spleen palpable 3 fingers below left costal margin and liver felt  $1\frac{1}{2}$  fingers below right costal margin. Icterus index of 15. Decreased fragility of erythrocytes which began at 0.36 and was not complete at 0.28. Blood counts are recorded in Table 2. Van den Bergh positive delayed.

This patient presents the typical picture of sickle-cell anemia without having developed any subjective symptoms of the disease up to the present time.

The remaining 3 patients showed no evidence of anemia, *i. e.*, are examples of sicklelema. Blood studies in these cases are recorded in Table 2.

TABLE 2.—BLOOD FINDINGS IN CASES 2 TO 5.

Case No.	Date.	Hemoglobin.	Red blood cells.	White blood cells.	Neutrophils.	Stab cells.	Segmented cells.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Reticulocytes in %.	Red blood cells morphology.
Case 2	4/18	58	4.150	6600	51	2	49	43	2	3	1	2.6	Aniso- poikilo- hypochromia, polychromasia. W. P. 100% sickling.
Case 2	7/21	66	4.730	9200	47	3	44	44	7	1	1	2	Aniso- poikilo- hypochromia, polychromasia. W. P. 100% sickling.
Case 3	4/18	84	4.610	9500	64	2	62	27	7	2		0.3	No abnormal cells. W. P. 100%.
Case 3	7/21	84	4.380	7700			58	34	7	1		0.2	W. P. 100%.
Case 4	5/20												W. P. 100%.
Case 4	8/5	94	4.900	7800	56	5	51	36	6	2		0.1	No abnormal cells. W. P. 100%.
Case 5	5/28												W. P. 100%.
Case 5	8/5	82	4.130	7600	53	2	51	39	6	2		0.2	W. P. 100% rare poikilocytosis.

W. P. = wet preparation for sickling.

CASE 3.—Mary A., aged 51, mother of the previous patient, was born in Naro, Italy. She has always been in excellent health and has had 4 children. Her appearance is that of a southern Italian, who does not appear older than her stated age. *Physical examination* is entirely negative. There was decreased fragility of erythrocytes which began 0.40 and was not complete at 0.28. Slightly delayed positive Van den Bergh.

CASE 4.—Jennie P., aged 26, a sister to the previous patient, born in Sicily and arrived in the United States at the age of 3 years. The significant facts in her history are that at the age of 14 years she suffered with an attack of appendicitis which was treated conservatively. Six years ago she had infectious polyarthritis with anemia of sufficient severity to require hospitalization. Three years later she had a second less severe attack. Except for fatigue while at work she is in excellent health. Examination reveals a rather obese female, fair complexion, straight brown hair; the heart is not enlarged, loud first sound, accentuated P2, no murmurs, abdomen is negative. There was decreased fragility of the erythrocytes which began at 0.38 and was not complete at 0.28.

CASE 5.—Charles P., aged 6 years, son of the previous patient was born in the United States. Past history of suppurative adenitis, measles and per-

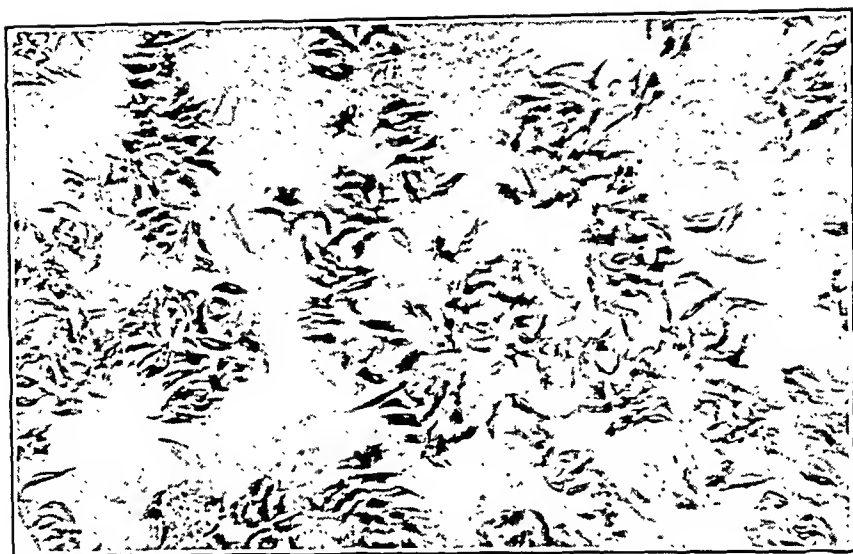


FIG. 1.—Micro-photographs of moist cover-slip preparations showing sickling in Case 1 (high dry power magnification).

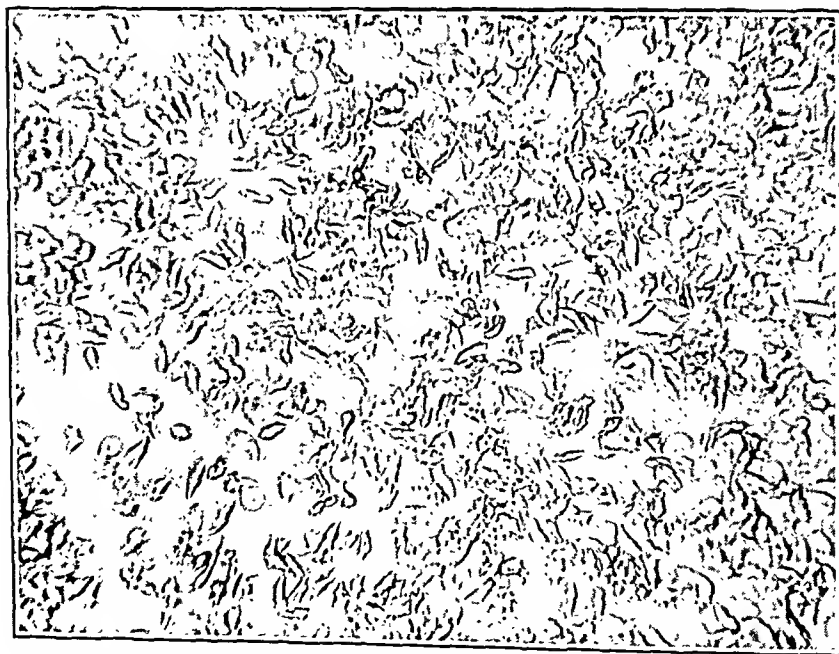


FIG. 2.—Micro-photographs of moist cover-slip preparations showing sickling in Case 2 (high dry power magnification).



tussis. At present he is in excellent health. Examination is entirely negative except for the presence of palpable post-cervical lymph nodes, hypertrophied tonsils and under-nutrition.

*Comment.* The sickling phenomenon is clearly demonstrated in 5 members of this white Italian family. The trait has been transmitted for three generations through the paternal branch of the family, whose ancestors inhabited Sicily. Most of the recorded cases in the white race appear to have their origin in this locality. Since it is known that this region is signally free from Negro inhabitants, it may be assumed that if there was any admixture of negroid blood, this must have occurred many centuries ago.<sup>6</sup>

The 5 cases can be classified into two groups. Those with anemia, or sickle-cell anemia, and those without anemia, or sicklemia.<sup>8b</sup> Cardoza<sup>4</sup> suggests that patients with sicklemia are potentially anemic and that those who are anemic may revert to the non-anemic phase. Our cases may be placed into three distinct divisions: 1, sickle-cell anemia with symptoms, Case 1, which presents the clinical and hematologic findings of sickle-cell anemia. It is worthy of note that the correct diagnosis was not made until the age of 22, although she had suffered from the disease according to the history since the age of 9. It was the consensus of opinion that she was suffering from some form of congenital or acquired hemolytic anemia from all the data referred to, but failure to demonstrate sickling left the actual diagnosis in doubt. It should be emphasized that with repeated careful technique of wet preparation, sickling may be easily demonstrated. 2, Sickle-cell anemia without symptoms, Case 2, who has definite anemia and splenomegaly. One may predict that a picture not unlike that of her sister may appear sometime in the future. The patient's age and the presence of splenomegaly raised the question of the value or advisability of splenectomy as a helpful therapeutic procedure. 3, The remaining 3 cases show the sickling trait without anemia. In addition to sickling, all the cases showed the constant finding of decreased fragility of the erythrocytes. Because of the dubious history of two episodes of infectious arthritis and anemia in Case 4, absence of residual cardiac findings, she might have possibly suffered from sickle-cell anemia crises on those occasions and is now in the stage of remission. Her son, Case 5, only 6 years of age, may be in the early phase of the disease in whom symptoms have not yet developed. The oldest member of the group may be an example of a case in the recovery phase. It has occurred to us that these groups may represent different phases of the same disease and that observations of similar cases over a period of several years may lead to valuable information and test the validity of this suggestion.

*Conclusions.* Two additional cases of sickle-cell anemia in a white Italian family are reported. The first case escaped detection for many years although symptoms were evident since the age of 9.

The second case is still asymptomatic. The entire group of 5 cases showed the sickling phenomenon and the constant finding of decreased fragility of the erythrocytes. It is emphasized that in obscure cases of hemolytic anemia in white patients, especially from Mediterranean countries, repeated wet preparations with careful technique should be applied. Because of the unusual opportunity presented in the study of this group which demonstrates various phases of the disease from its active to the latent stages, the suggestion is advanced that those having the sickle-cell trait represent patients with sickle-cell anemia in one of its phases.

We wish to express our sincerest gratitude to Prof. Linn J. Boyd of the Department of Medicine, for his permission to report these cases and for his many valuable suggestions.

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## THE EFFECT OF STORAGE ON THE PROTHROMBIN CONTENT OF CITRATED BLOOD.

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TRANSFUSION of blood is an established adjunct to vitamin K therapy for maintaining or restoring safe concentrations of prothrombin. Recently, Rhoads and Panzer<sup>4</sup> concluded that storage of blood diminishes the concentration of prothrombin and impairs its value for treatment of hemorrhage due to prothrombin deficiency.

Transfusion of blood stored a week or more, according to these authors, would be practically useless for the purpose of increasing prothrombin. Only fresh blood would be considered suitable. In disagreement with this view, is the work of DeGowin, Harris and Plass<sup>2</sup> who found, using the prothrombin method of Smith, Brinkhous and Warner, that "prothrombin is not seriously impaired by 2 weeks storage."

Because of the wide use and ready availability of stored blood for transfusion, many hospitals have installed blood banks. It seemed important, therefore, to secure additional information concerning the stability of prothrombin in preserved blood.

**Method.** Fifteen cubic centimeter samples of blood contributed to the blood bank of the Philadelphia General Hospital were measured into 30 cc. wide mouth bottles, stoppered and stored in the refrigerator at 5° C. under the same condition as the main portion of the blood. Bottles of this size exposed relatively the same surface area to the air as was exposed in the Erlenmeyer flasks in which blood was preserved. One-tenth volume of 2.5% sodium citrate added to the blood when collected served as anti-coagulant. Prothrombin and certain other constituents were measured in triplicate in the blood specimens at 3- to 7-day intervals for 3 to 5½ weeks. Quick's method<sup>3</sup> was employed for determination of prothrombin. It was found that this method could be applied to citrated blood with results comparable to those obtained by use of oxalated specimens. Thromboplastin was prepared from rabbit brain and was assayed before each run by means of normal human plasma. Since most preparations of thromboplastin failed to cause normal plasma to clot in the average time of 12.5 seconds found by Quick, results have been corrected by the following formula:

$$\frac{\text{Prothrombin time on first day}}{12.5} \times \text{prothrombin time after storage} = \text{corrected prothrombin time.}$$
 The corrected time was converted to per cent of normal prothrombin by means of the graph published by Quick.<sup>3</sup>

TABLE 1.—PROTHROMBIN VALUES OF STORED BLOOD.

Spec. No.	Prothrombin, % of original value.						
	Days stored: 0.	3.	6-8.	13-17.	21-22.	28-29.	32-39.
1 . . . .	100	75	48	18	16		
2 . . . .	100	50	32	32			
3 . . . .	100	70	34	31	27		
5 . . . .	100	..	100	100	60	70	
6 . . . .	100	..	42	38	32	42	38
7 . . . .	100	..	44	44	44	55	44
8 . . . .	100	..	70	70	..	70	36
9 . . . .	100	..	100	100	90	55	45
10 . . . .	100	..	60	50	90	..	50
			(9 da.)				
11 . . . .	100	..	..	42	60	..	55
12 . . . .	100	60	50	40			
13 . . . .	100	100	60	43			
14 . . . .	100	60	45	47			
15 . . . .	100	85	40	40			
16 . . . .	100	65	45	38			
17 . . . .	100	90	52	35			
Average . . . .	..	73	55	48			



# REINHOLD, VALENTINE, FERGUSON:

TABLE 2.—PROTHROMBIN VALUES OF PRESERVED BLOOD.

Spec. No.	Day of storage.	Prothrombin time (in sec.).	Per cent of normal.
3 (Apr. 21-May 10)	1	14	100
	3	16	70
	6	24	31
	7	21	36
	13	24	31
5 (Apr. 25-May 22)	19	26	27
	1	24	100
	7	18	200
	14	24	100
	21	28	60
6 (May 2-June 9)	28	17	70
	1	24	100
	8	26	42
	14	27	38
	21	24	32
7 (May 2-June 9)	28	26	42
	39	15	38
	1	20	100
	8	20	44
	14	20	44
8 (May 5-June 9)	21	18	55
	28	20	44
	39	21	100
	1	23	70
	6	23	70
9 (May 5-June 9)	15	23	30
	28	35	100
	35	20	100
	1	20	100
	6	21	90
12 (May 30-June 12)	15	21	55
	21	24	45
	28	27	100
	35	20	60
	1	23	50
13 (May 30-June 12)	3	26	40
	7	29	100
	13	18	100
	1	18	60
	3	21	43
14 (May 30-June 12)	7	24	100
	13	18	60
	1	21	45
	3	25	47
	7	24	100
15 (May 30-June 12)	13	16	85
	1	17	40
	3	23	40
	7	23	100
	14	17	65
16 (May 30-June 12)	1	19	45
	3	23	38
	7	25	100
	14	16	90
	1	17	52
17 (May 30-June 12)	3	20	35
	7	24	
	14		

**Results.** Prothrombin concentration of stored blood decreased moderately (to 73%) within 3 days. Three of 9 specimens were unchanged at this time. The most marked alteration was a decrease to 50%. At 6 to 7 days a further decrease to an average of 55% was observed. Several specimens were still unchanged at this time; however, half had fallen to less than 50%. Further preservation led to continued gradual decline in prothrombin; three-fourths showed less than 50% at 13 to 17 days. Seven specimens showed little or no hemolysis for longer periods, and it may be significant that in these, suitable in appearance for transfusion, the prothrombin concentration remained at an average of 52, 48 and 53% respectively at 3, 4 and 5 weeks.

Whether preserved blood can be utilized to increase prothrombin concentration of blood of patients showing prothrombin deficiency is a matter of considerable practical importance in hospitals relying upon the blood banks. It would appear that although prothrombin concentration decreases with the duration of preservation, it still is preserved in amount sufficient to increase by a significant amount the concentration in the blood of the recipient. Thus, if a transfusion of 500 cc. of blood stored 3 days was given to a patient with blood volume of 7000 cc. and a prothrombin of 15%, one would be adding 250 cc. plasma of concentration of approximately 75% of the normal prothrombin. This would raise the prothrombin percentage of the recipient to about 19%, whereas a transfusion of equal amount of fresh blood with concentration of 100% prothrombin would raise the recipient's prothrombin to 20.6%. If larger volumes of blood are given by transfusion, the increase in prothrombin percentage in the recipient is naturally more rapid when fresh blood of normal prothrombin concentration is given. Thus, if 1000 cc. of blood is given to a patient with prothrombin time of 15%, prothrombin concentration would rise to 26.5% if fresh blood of 100% prothrombin is given, whereas it would rise to 22.5% if stored blood of 75% prothrombin is used. In the same way, if 1500 cc. of blood is given with prothrombin concentrations as mentioned above, the recipient's eventual prothrombin would be elevated to 36.5% with 100% blood and 25.6% with 75% blood. These calculations are based on the assumption that beneficial effects of transfusion depend entirely upon addition of prothrombin. However, it seems highly probable that the transfusion *per se* may be a factor in the elevation of prothrombin. This is suggested in the protocol of Quick's patient<sup>3</sup> whose prothrombin was 8% before a transfusion of 550 cc. of blood and rose to 20% immediately after the transfusion. This effect of transfusion *per se* on the prothrombin concentration of the recipient is a problem which we are investigating as the occasion arises.

In the blood bank at this hospital, where from 40 to 60 transfusions are given per week, 90% of the blood preserved in the bank is held

2 days or less. In this period the concentration of prothrombin decreases so little that preserved blood can be used effectively in treating prothrombin deficiency. With the considerable individual variation that occurs, however, the efficiency of even relatively fresh blood may be significantly lowered in individual cases. Preserved blood may be of value after longer periods of preservation, since we have found that bloods that are preserved without hemolysis maintain their prothrombin concentrations fairly well. Bloods retained longest in the bank are those of the less common Types I and III (Moss). In spite of the fact that the prothrombin content may be lower in such bloods, it may still be sufficiently high to be of value, especially when easily available in the blood bank. This is true particularly when volunteer donors must be depended upon as is the case in most large municipal hospitals.

**Conclusion.** The incentive to this study was provided by the appearance of articles suggesting that preserved blood was of doubtful value in treatment of patients with prothrombin deficiencies. Our clinical experience with the use of preserved blood in such cases has been uniformly favorable, especially if not more than 3 days old. The value of the blood bank idea has been so impressed upon us that it seemed worth while to defend its use under these circumstances.

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## THE RÔLE OF WATER BALANCE IN THE CLINICAL MANIFESTATIONS OF ALLERGY.\*

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ALLERGIC phenomena in a human subject occur when that subject is exposed to a specific allergen to which he happens to be sensitive. The same phenomena, or phenomena so similar as to be indistinguishable, at times occur in the same patient under circumstances in which a non-allergic factor appears to be the causative agent. For example, a patient experiences an attack of migraine after eating a certain food. The patient also regularly suffers the same kind of an attack each month at the onset of her menstrual period, and without having eaten the known food allergen. Or, a group

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of asthmatics, each one sensitive to different allergens, all develop exacerbations on the same day, when high winds presage the onset of a storm. The possible manner in which these non-allergic factors might cause phenomena that are apparently the same as those provoked by exposure to an allergen has given rise to a number of widely differing theories. Some of these theories have led their proponents into error, when they fallaciously applied them to explain the mechanism of the allergic phenomenon itself. It is the purpose of this paper to point out some examples of such fallacious reasoning and to present evidence for an acceptable explanation.

I shall begin with one of my own mistakes. In 1934, I published some observations on a curious interrelation between allergy and diabetes.<sup>7</sup> Allergy and diabetes rarely occur in the same individual *at the same time*. Yet a study of the history of a large number of diabetics revealed that they have a much higher family incidence of allergy than do non-diabetics and that diabetics themselves give a past history of allergic complaints much oftener than do a control group. This led me to suggest that in allergy there may be operative an endocrine factor which stands in reciprocal relationship to the endocrine factor in diabetes: that is, hypofunction of the adrenals.

It is a common experience that asthma, urticaria and migraine may occur in close relationship to the menses. In many instances the allergic phenomena cease after the menopause. Occasionally some form of opotherapy, usually pituitary or ovarian, tends to relieve the allergy at the menses. Consequently a gonad factor has been suggested as playing a rôle in the mechanism of such allergies.

Pregnancy may often profoundly influence the course of an allergic disease. Unfortunately from the standpoint of an ovarian theory, the effect is not always in the same direction. Some patients are free of their asthma or hay fever during the whole of the pregnancy, while others at that time suffer an exacerbation of their allergic complaint.

Leaving the endocrine organs for a moment, let us turn to some chemical theories. For some years Beckman<sup>2</sup> has been enthusiastic about the therapeutic effect of large doses of nitro-hydrochloric acid in allergic conditions, especially hay fever. Although results in the experience of others have been by no means as good as those claimed by Beckman, the fact remains that an occasional case is strikingly benefited. This led Beckman to conclude that all allergy is fundamentally an alkalosis.

Potassium has from time to time been brought into the allergic picture. At first there was the view that a disturbed potassium-calcium ratio in the body economy was the important thing. More recently have come observations on the effect of potassium in relieving a number of allergic conditions. Following the lead of Barker,<sup>1</sup> who reported the disappearance of edema of cardiac or

nephrotic origin in a number of patients placed on a high-potassium low-sodium regimen, Rusk and Newman<sup>11</sup> found the same procedure helpful in a case of portal cirrhosis with edema. Then Rusk and Kenamore<sup>10</sup> applied the same measure to another form of edema, localized and circumscribed in the skin, urticaria. Finally, Bloom<sup>3</sup> published some statistics of remarkable results from such a treatment of pollinosis, both hay fever and asthma; also in chronic asthma, allergic rhinitis, eczema, urticaria, migraine and even nasal mucous polyps. Although others have failed to get the excellent results claimed by Bloom, nevertheless some patients are helped to a surprising degree by potassium chloride, although only too often that result is temporary. But Bloom, losing sight of Barker's original point that potassium acted by producing a generalized reduction of body fluid, jumped to the conclusion that potassium plays the major rôle in the mechanism of allergy itself. Thus he suggests that proteins can bring about the manifestations of allergy only when the underlying electrolyte mechanism is disturbed.

And now to return to the effect of storms on asthma. It is a common experience in all allergy clinics that on certain days a large number of asthmatics will report a sharp exacerbation of symptoms, irrespective of the differences in the types of allergens to which they happen to be sensitive. This usually happens on a day when a severe storm is approaching. On my office-desk is a barometer: whenever there is a sharp fall in pressure, I can confidently expect a wave of increased asthma among the chronic asthmatics, and the steeper the gradient of the fall, the worse the asthma. Sharp falls in barometric pressure bring with them high winds. The Simon-pure allergist therefore seeks to explain the increased asthma by increased contact with air-borne allergens that the wind stirs up. Here, then, are a number of factors, apparently differing widely from one another, and yet having a pronounced effect, some in the production, others in the relief of allergic phenomena. Is there anything which these factors have in common? I believe there is. Each one involves a more or less pronounced shift in water balance. Let us examine the evidence.

It is a well-established fact that in diabetes there is a tendency to dehydration. The loss of sugar and of increased amounts of sodium chloride in the urine plays an important part in this connection. An added factor is the reduction of glycogen stores in liver, muscles and even the skin, resulting in a loss of much intracellular water. The more severe the diabetes, the greater is the dehydration, even before yet another dehydrating factor, acidosis, comes into play.

The menstrual cycle is attended by fluctuations in water balance that may reach considerable proportions. During the day or two preceding, and the most of the menstrual period, the posterior lobe of the pituitary produces increased amounts of an antidiuretic

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substance, as a result of which a positive water balance results, with the retention at times of considerable amounts of water. In 1938, Thorn, Nelson and Thorn<sup>14</sup> reported their observations on menstrual edema in a series of 50 student nurses in the Johns Hopkins Hospital. Of the 50 subjects no less than 24 showed a total water retention of at least 2 liters and some of them as much as 4 liters. With the cessation of the antidiuretic activity of the pituitary toward the end of the period, and perhaps under the influence of other gonad factors, this excess water is lost and the normal balance is reestablished.

In pregnancy there is no constant trend with regard to water balance. Griffith,<sup>6</sup> in our Cardiovascular Section, has found that some patients show an increase of pituitary antidiuretic factor, whereas others show a normal or a diminished amount. There would consequently be no constant effect on water balance.

Acidosis produces a marked loss of body fluid, whether the acidosis is due to disordered metabolism as in diabetes, or to the administration of large amounts of an acid, such as hydrochloric acid. In each instance large amounts of base excreted in the urine account for the loss of much body water. Myerson<sup>9</sup> and Loveless<sup>8</sup> have suggested that the benefit experienced by some allergic patients from acid therapy is due to the diuresis and dehydration produced.

Potassium in the body occurs chiefly within the cells where it binds much of the intracellular water. Sodium, on the other hand, is mostly extracellular and so influences the amount of interstitial fluid. The administration of large amounts of a potassium salt produces first an increase of intracellular water at the expense of interstitial water. In addition, there results a displacement of sodium ions with consequent increased excretion of sodium chloride and water in the urine. The net result is a decrease in total body water.

And how do storms figure in water balance? In the study of the effects of low barometric pressure on dogs and rats, Smith<sup>13</sup> found a definite retention of water. The studies were carried out in a chamber in which pressures were reduced over 48-hour periods in amounts ranging from 2.6 to 9.8 cm. of mercury, figures that are well within the range of human experience. Not only did the animals retain water, but they were obviously restless. Smith suggests that this hydration may be the mechanism of inducing a variety of reactions on the part of many animals and some people with approaching weather changes.

How may these various facts be brought into relation with allergic phenomena?

A basic component of the allergic reaction is edema in the shock organ. The production of this allergic edema involves a quantitative factor. Let us assume that in a given patient the figure 100 represents the amount of allergenic action required to produce shock

organ edema and consequent symptoms. Then if the patient is subjected to an allergenic action of a magnitude of only 95, no edema and no symptoms result. But if he is subjected to allergenic action in an amount of 105, then edema and symptoms are produced.

Now let us suppose that in addition to the allergenic impetus to edema, there appears on the scene a factor that influences water retention, and therefore tends to facilitate the production of edema: then it will enhance the effect of the allergenic action. A patient, subjected to an allergenic action of 95, in itself insufficient to produce allergic edema, will develop edema in the shock organ if in addition she is subjected to another type of edema producer, such as the water retention incident to the menses, let us say in the magnitude of 10. Or, the 10 additional points of edema production may be provided by the water retention incident to the fall in barometric pressure before the storm.

Conversely, the patient who is experiencing edema of his shock organ and consequent symptoms due to an allergenic action of the magnitude of 105 would experience a regression of shock-organ edema and symptoms when an anti-edema factor of a magnitude of 10 comes into play. The anti-edema factor might be the dehydration of diabetes, or of acidosis, or that following the administration of potassium chloride.

I have assigned large values to the allergenic action for producing edema and comparatively small ones to the other factors influencing edema. That is because the edema produced by allergenic action, although trifling as to the actual amount of water involved, is concentrated in one small structure, the shock organ. The effect on water balance produced by other factors, on the contrary, is a generalized one in which the shock organ participates to no greater degree than does any other tissue. Thus, when the factor causes generalized edema, even though the body as a whole may be retaining several liters of water, the amount that is apportioned to the shock organ is bound to be much less than that which allergenic action can localize there.

Consequently, if the allergenic cause of shock organ edema were intense, for instance of a magnitude of 200, then a non-allergic general edema-producing factor of a value of 10 could not greatly aggravate the edema in the shock organ. What is more important, a non-allergic anti-edema factor of a value of 10 could certainly not completely relieve the patient's symptoms.

To carry this thought yet farther: the general non-allergic factors could probably never produce a sufficient water retention, and in a short enough time, to give rise to a sufficiently severe and suddenly produced edema in a given area to result in symptoms resembling an allergic phenomenon. The only conditions that might be looked on as exceptions to this view are the convulsions (cerebral edema) of acute water intoxication, and the asthmatoïd symptoms

that may result when the bronchial tree is subjected to the acute intense inflammatory edema that follows exposure to diazomethane, and certain gases used in warfare.

The concept, then, which I wish to propose is that in allergic persons, symptoms may be the result of the concerted action of two causes of edema, the one (allergenic) acting locally in the shock organ, the other a cause of generalized hydration. The important one as to magnitude of local effect is the allergenic factor. Less important as to magnitude, but at times the only *obvious* factor, may be any one of several causes of water retention. Conversely, in allergic persons symptoms may be relieved when some cause of generalized dehydration can sufficiently reduce the edema in the shock organ. The acceptance of such a view would serve to set aside as fallacious a number of theories which some have proposed to explain the mechanism of allergy itself, but which most of us have been loath to accept.

Thus, I was right in my observation that diabetes in some way acts favorably on the allergic state. It is also true that diabetes depends fundamentally on an endocrine mechanism, predominantly pancreatic. But I was wrong in assuming that therefore the allergic state must also be dependent on an endocrine mechanism, probably adrenal. One must at least admit the possibility that water balance changes could equally well explain the facts.

(Parenthetically, mine was, of course, only one of numerous attempts to incriminate the adrenals. Many have sought to prove that adrenal hypofunction is at the bottom of all allergy. The efficacy of epinephrine in relieving allergic symptoms gave the first impetus to such a view. It has prompted the search for methods that might disclose an abnormally low blood content of epinephrine. Yet if that were found, it could just as well be an effect—exhaustion from overdemand—as a cause of allergy. Suggestive experimental evidence is furnished by the fact that rats, ordinarily so hard to sensitize, may be fairly readily sensitized after their adrenals have been removed. Yet in man, as far as I know, *no* active allergy occurs, let alone an increase in sensitivity, in Addison's disease. Why? Perhaps because of the marked sodium loss and dehydration in that condition? At all events, one must admit that an adrenal etiology of allergy is just as far or farther from being proved as it ever was.)

Beckman was right, although overenthusiastic, when he noted that the production of an acidosis could relieve allergic symptoms. But he was not justified in assuming that alkalosis could have been the only cause, for he, too, overlooked the added possibility that dehydration could explain his results. Let it be remembered that, although an induced acidosis will lessen or temporarily stop epileptic seizures, no one suggests that epilepsy is therefore due primarily to



alkalosis: It is recognized that the dehydration incident to acidosis exercises a purely non-specific effect in combating a cortical edema.

Bloom fell into the same error when he assumed that the potassium effect proved that potassium played a rôle in the basic mechanism of allergy. But he compounded the felony when he further assumed that, because the administration of potassium relieved allergic symptoms, a general somatic shift of electrolytes must necessarily have preceded the symptoms. There is available some evidence, to be cited later, which suggests that symptoms begin in the presence of a normal water balance, but that after symptoms have started, there is a shift in the direction of water loss by which the body seeks to relieve the allergic edema.

Now let me cite a case which illustrates two important points. In the first place, it shows that this concept of the concerted action of two causes of edema in the production of symptoms is applicable in other fields of medicine. In the second place, it makes it easy to demonstrate the fallacy in reasoning of which some of us have been guilty.

Edeiken and Griffith<sup>5</sup> have recently reported their observations in a woman with mitral stenosis of rheumatic origin. Her cardiac function for nearly a year has been just on the verge of inadequacy. Each month, with the onset of her menstrual period, she rapidly developed cough, dyspnea and the signs of severe pulmonary edema. On the theory that her attacks of acute cardiac decompensation were precipitated by the water retention incident to the menses, Dr. Edeiken gave the patient mercupurin just before each period to promote diuresis. This resulted in practically complete prevention of her usual attacks. For several months this was repeated with the same good effect. The next development in the case is even more interesting. Studies of the patient by Dr. Griffith showed that during the menstrual period her blood contained a considerable quantity of the antidiuretic factor formed by the posterior lobe of the pituitary. Since it is known that irradiation of the pituitary can produce a sharp diminution in this function of the gland, the patient was subjected to such Roentgen therapy. There resulted the expected drop in production of the antidiuretic substance and the patient has now gone through seven periods without decompensation and without the help of mercupurin. Here menstrual water retention and heart failure collaborated to produce pulmonary edema.

And now for the matter of fallacious reasoning: When an allergist concludes that because a patient's allergic symptoms occur regularly with the menses there must necessarily be an endocrine factor in the mechanism and production of her allergy, he is just as wrong as if Edeiken and Griffith had concluded that an endocrine factor was involved in the production of their patient's mitral stenosis. Even though potassium chloride helped relieve the ascites in Barker's

cases of cardiac and nephrotic edema, he never thought of suggesting that a defect in potassium economy was responsible for the cardiac or renal disease. No more should one postulate such a defect in potassium economy as essential to the production of allergy, merely on the evidence that potassium administration can relieve allergic symptoms.

Let me cite another instance in which two factors, in no wise related to each other, the one a producer of water retention, the other a local scar, combined to produce symptoms referable to a very restricted part of the body. I am indebted to Dr. O. H. Perry Pepper for permission to refer to his patient. A girl, now 16 years old, had suffered a birth trauma that left her with certain muscular defects. At the age of 11 she began to have seizures of a frank epileptiform type but without loss of consciousness. These led to an operation by Dr. Charles Frazier, who successfully removed a brain cyst that was evidently a residuum of her birth trauma. There followed complete relief from the epileptic attacks. Two years later, when she was 13, her menses began. During the next 3 years with each menstrual period she had attacks of intense headache, rigidity of the neck and muscle tenseness which apparently stopped just short of epileptic convulsions. Dr. Pepper suspected that two factors were responsible for these attacks: menstrual edema, and localized intracranial post-traumatic scar tissue, as a result of which a relatively small degree of brain edema could exert undue pressure in certain cortical areas. An assay of pituitary antidiuretic factor in her serum by Dr. Griffith showed an increase of this substance during the menstrual period. Her pituitary was therefore irradiated, the dosage being 50 R. As a result she has gone through three periods without an attack.

The question arises, is there perhaps a defect in water balance in allergy itself? There are as yet very few direct observations on this subject but they are, in my opinion, highly significant.

In 1938, Cook and Stoesser<sup>4a</sup> reported that artificial fever in asthmatics was usually followed by remission of symptoms when the sodium chloride content of the diet was extremely low, but not when the intake of this salt was unrestricted. In 1 case, 4 gm. of sodium chloride were administered when the patient had been free of asthma for 10 days, "all other factors remaining constant," and the asthma promptly recurred.

They also made 20 observations on 6 patients who were *kept on a low-sodium chloride diet* and to whom they gave pitressin to produce water retention. In the preliminary control periods of all 20 observations the patients had asthma. During the pitressin hydration (which involved an increase of 2 to 5% in body weight) the patients had less asthma than in the preceding control period. The authors conclude that the sodium ion may exercise an adverse influence on the asthmatic patient, independent of its usual relation to hydration.

In 1939, these same authors<sup>4b</sup> reported further observations along the same lines. In addition, they gave potassium chloride to asthmatic patients on a low-sodium chloride diet and observed a cessation of asthma in milder cases. Again they conclude: "It would appear that the sodium, potassium and water metabolism bear an important relationship to the asthmatic state."

It would appear to me that these authors may be on the verge of committing the same type of fallacy as previously mentioned, if they were now definitely to conclude that because sodium, potassium and water metabolism influence the asthmatic state, then in the asthmatic state there must necessarily be an abnormal metabolism of sodium, potassium and water, and that such an abnormal electrolyte metabolism is an essential part of the intrinsic mechanism of asthma. *Non sequitur*.

However, their observations call attention to another phase of the relation of water balance to the development of allergic phenomena: the site in which body water is localized.

Sodium salts are found primarily extracellularly and therefore influence the amount of interstitial fluid. If sodium be withheld from the diet, then even though there be an increase of total body fluid (hydration after pitressin), there will be no abnormally large amount of interstitial fluid. Interstitial water is that which is primarily involved in the production of edema: edema might even be defined as being essentially an excess of *interstitial* fluid. Pitressin hydration therefore will not produce edema as easily when sodium is withheld as it would when sodium is freely given. The tendency to allergic edema, *e. g.*, asthma, is therefore also lessened when sodium is withheld and is increased when sodium intake is increased. Within certain limits this is true, irrespective of the total amount of water in the body.

Potassium salts are found primarily intracellularly and therefore influence the amount of intracellular fluid. An increased intake of potassium would first of all cause an increase of intracellular fluid at the expense of interstitial fluid. In case of an excess of interstitial fluid (edema), potassium administration would cause a diminution of the interstitial fluid (edema). It could therefore also diminish an allergic edema, and, as Cook and Stoesser found, it could even relieve symptoms (asthma) "*in milder cases*," that is, in cases in which the allergic factor producing edema is just strong enough to produce edema of the shock organ.

But in allergic edema the major factor in the production of edema of the shock organ is still the allergic phenomenon itself. *In the presence of the allergic factor*, an increase of sodium intake can increase the edema of the shock organ, even to the production of symptoms when the allergenic cause is just infra-threshold in degree; whereas a restriction of sodium intake or an increase of potassium intake will tend to lessen the amount of interstitial water and con-

sequently the edema of the shock organ, even to the relief of symptoms when the allergenic cause is just supra-threshold in degree. But if the allergenic cause is present far above the edema threshold in degree, then variations in neither sodium nor potassium intake can sufficiently influence the edema of the shock organ to be clinically apparent. Also, *in the absence of the allergenic factor*, no increase, however great, of sodium can produce a localized edema with resultant symptoms of the kind which characterize the clinical manifestations of allergy.

In 1939, Sheldon, Howes and Stuart<sup>12</sup> published their studies on total water and sodium exchanges in asthmatic patients. Their subjects were 5 males, 3 of whom were known to develop asthma whenever they ate certain foods, and 2 were sensitive to ragweed pollen. Four patients were observed while on a constant intake of food, water, sodium and potassium. Water and salt excretion were measured, including a careful check on body weight. The patients were symptom-free for an initial control period. Asthma was then induced by feeding the allergenic food or by the insufflation of ragweed pollen into the upper respiratory tract.

During the control period all patients were in balance as to water and salt metabolism. With the production of asthma there promptly developed in each patient an increased output of water and sodium chloride. The total loss of body water associated with an asthmatic attack varied from 737 to 2013 gm. The water metabolism paralleled that of the sodium. *The water balance was negative from the start of the asthma*, in spite of distinct edema of the shock organ.

These data I believe to be highly significant. In the first place, there is no evidence of any water retention in the body as a whole, even in the early stages of the asthmatic attack. Yet if potassium deficiency and sodium excess were an intrinsic part of the mechanism of an allergic response, one would expect some evidence of an initial hydration of the body as a whole. If, in spite of no initial general hydration, one would still wish to ascribe the edema of the shock organ to potassium-sodium effects alone, then one would have to postulate one kind of electrolyte metabolism in the shock organ and a different one in the rest of the body, an obvious inconsistency. The allergic edema of the shock organ is therefore probably determined in the first instance by factors other than electrolyte balances alone.

In the second place, the water and sodium loss of these patients continued unabated until the attack was over. Then there was a retention of both water and sodium. In my opinion these facts, far from suggesting, as they have to some, that excess of sodium and water and possibly deficiency of potassium in the body are part of the mechanism of allergy, would appear, on the contrary, to be good evidence that increased excretion of water and sodium is simply a part of the body's defense mechanism. It is an attempt,

by means of a general depletion of body fluid, favorably to influence the localized shock organ edema that an allergic reaction has produced.

I wish to refer briefly to some of our clinical experiences which lend additional support to our thesis.

We have used potassium chloride in patients with hay fever, perennial allergic rhinitis and asthma. I will cite no figures as to results; they will be reported elsewhere. But the trend of those figures appears to show the following things: By no means all patients, not even a sizeable minority, were helped by potassium chloride alone. The addition of potassium chloride to other types of therapy distinctly improved results in some cases. The impression was that milder cases, patients just over the threshold of symptoms and with sensitivities that appeared to be neither extensive nor intense, were the most likely to show improvement on potassium chloride. In patients with severe and multiple sensitivities there was no effect. Thus, of 2 patients, brother and sister, the brother with rather mild hay fever and no asthma experienced complete relief of symptoms on potassium chloride alone. The sister, with severe pollen asthma as well as hay fever and some perennial symptoms, including eczema, experienced no relief in any phase of her troubles. The non-specific effect of potassium chloride dehydration would therefore appear to be adequate to give relief of symptoms only in the less intense types of allergic edema of a shock organ.

A second point of interest in the potassium chloride effects was seen in some cases of perennial allergic rhinitis. After a week or so of considerable improvement, symptoms recurred in spite of continuation of treatment, suggesting that the allergic edema of the shock organ had reestablished itself at the new lower level of water balance.

In several women with migraine and one with mild asthma, all of whom complained of menstrual exacerbations, the simple expedient of sharp restriction of salt and water intake for several days before and during the period gave striking relief from the attacks usually experienced at the menses.

One is tempted to speculate as to possible further applications of the theory here propounded. That, however, would be unwise at this time. Rather should our efforts be turned in the direction of getting more facts. Clinical studies should prove particularly fruitful, provided they are properly controlled. Here is a new wide field for careful investigation and for still more careful thinking.

In summary, then, the theory is suggested that changes in the water balance of the body may influence the occurrence of allergic phenomena. Water and salt retention will favor the development of allergic reactions. Dehydration and salt loss will antagonize allergic reactions. Increased intake of sodium, by tending to increase

interstitial fluid and edema, will also favor the development of allergic reactions. Increased intake of potassium, or decreased intake of sodium, by tending to increase intracellular fluid and to decrease interstitial fluid and edema, will antagonize allergic reactions. Such shifts in water balance occur clinically in a variety of conditions, or they may be induced by a number of therapeutic measures. The effect of hydration and dehydration on allergic reactions is purely non-specific. Consequently the causes initiating changes in water balance must not have attributed to them any specific etiologic significance in the causation of the allergy itself. The production of the allergic phenomenon of edema in the shock organ is a thing apart: its mechanism, in the last analysis, is still a mystery.

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## ELECTROCARDIOGRAPHIC AND SERUM POTASSIUM CHANGES IN FAMILIAL PERIODIC PARALYSIS.

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FAMILIAL periodic paralysis has been the subject of many reports, which were reviewed by Schoenthal in 1934.<sup>16</sup> It has long appeared that the paralytic manifestations of this disease were related to the potassium metabolism. Holtzapple<sup>9</sup> was of the opinion that potassium bromide was effective in treating the paralytic state. He attributed this to its sedative action. A number of observers have recorded the level of potassium in the blood serum in this dis-

ease.<sup>1,2,5,7,15</sup> Gammon, Austin, Blithe, and Reid<sup>8</sup> state that during severe spontaneous paralyses, the serum potassium level has been found to fall as much as 30%, while in mild attacks the fall may be only 5 to 10%, with values of 4.79 milliequivalents per liter (18.6 mg. per 100 cc.). The intravenous administration of potassium salts to experimental animals was found by Mathison<sup>12</sup> to induce ventricular fibrillation. Nahum and Hoff<sup>14</sup> showed that the mechanism of this process was the production of widespread block in all parts of the heart and stimulation of the automaticity of the pacemaker. Winkler, Hoff and Smith<sup>19b</sup> in a recent paper dealing with the effect of potassium salts and of a mixture of potassium and calcium salts in animals concluded that the "toxic effects of potassium on the heart are due to some highly specific effect on that organ which is not shared by skeletal muscles generally." Further, with respect to potassium, Thomson<sup>17</sup> has described the electrocardiographic changes in patients suffering from Addison's disease and found that rise in the level of serum potassium is accompanied by increase in the amplitude of the T wave, followed in some cases by decrease in amplitude when the level fell as a consequence of treatment. There have been no reports of the electrocardiographic changes in a state of low potassium concentration in either experimental animals or human beings. In a survey of the literature we have found one report only in which electrocardiographic changes were recorded in familial periodic paralysis (Janota and Weber<sup>10</sup>). In this case, however, correlation with the level of serum potassium was not made. We have had the opportunity of following the serial changes in the electrocardiograms of a patient suffering from familial periodic paralysis during an attack, when the serum potassium was low. These observations will now be recorded.

**Clinical History.** The patient, a 19-year-old male, white laborer, was admitted to this hospital on June 18, 1939. His complaint was paralysis of all muscles below the neck of 3 days' duration. His father had experienced similar attacks of paralysis which were diagnosed in 1918 as familial periodic paralysis. The patient had suffered no serious childhood or adult illnesses. He denied venereal infection. His general health had been good.

The patient suffered a first attack of paralysis in the muscles of the trunk and extremities in late December, 1935, when he awakened one night and was unable to turn over in bed. His father tested him with a pin point and found that sensation was intact. The patient had two similar attacks in the next several weeks both terminating spontaneously. During February, 1936, he was studied at this hospital. Paralysis, however, did not occur at that time.<sup>13</sup>

From February, 1936, to June, 1939, the patient experienced approximately 20 paralytic attacks. These did not occur in a cycle; they varied in severity and in duration from several hours to 3 days. The day before the attack which we are now reporting, he ate a large amount of carbohydrate and engaged in an unusual amount of activity. When he awakened the next morning, he was unable to move his head, arms, or legs, and experienced anorexia, nausea and some retching. For the 24 hours before his admission he had been unable to defecate and had some slight difficulty

in micturition. He was brought to the hospital because paralysis had then continued for 3 days, his speech had developed a peculiar quality and swallowing was difficult. The patient reported that his breathing felt impaired and for about 24 hours before admission he was conscious of pounding of the heart.

*Examination.* The temperature was 37.8° (rectal), pulse 90, respirations 20, and the blood pressure 125/68. The patient was a muscular and well-nourished individual. He was flaccid below the neck. Respiratory movements were slightly labored and were made with the aid of the accessory muscles. The diaphragm appeared not to be involved. The only voluntary movement which the patient could make below the level of the neck was a slight motion of the thumbs and index fingers. Speech was slurred and of a monotonous character and swallowing was difficult. The head including the eyes, ears, nose and throat, and the neck were essentially normal. The lungs were clear throughout to percussion and auscultation. The point of maximum impulse and the left border of dullness of the heart were 7 cm. from the midsternal line in the fifth left intercostal space. There was no precordial shock or thrill. The heart sounds were loud; normal sinus rhythm prevailed. A coarse systolic murmur was heard over the whole precordium and the second sound in the mitral area was reduplicated. There were no signs of congestive heart failure. The abdomen exhibited no abnormalities. There was complete absence of all reflexes except those of the pupils and jaw. Sensibility for all the modalities was normal. During the course of our observations, the patient received 2 doses of potassium chloride of 4.2 gm. each. These were administered by mouth 1 hour and 50 minutes apart. He showed a gradual return of muscle function and during this time observations relating to the heart were made. Nine hours after his admission, the patient was able to move all parts, regaining voluntary muscle function most dramatically over the last 10 minutes of the period of paralysis. He was then able to feed himself and be out of bed. Reduplication of the second sound in the mitral area and the apical systolic murmur persisted. Normal sinus rhythm was still present. The patient was discharged on June 19, 1939, approximately 12 hours after admission because he wished to return to work.

*Observations.* An electrocardiogram which had been taken during the patient's earlier hospital admission served as a control. A series of three records was made during the attack of paralysis which we observed (Table 1): the first immediately on admission; the second and third, 85 and 110 minutes respectively, after giving potassium chloride, and the fourth the morning after recovery from paralysis; another, 4 months later was an additional control. Samples of blood were drawn immediately after each electrocardiogram had been taken for estimations of the level of certain ions and of serum choline esterase activity. Serum potassium was determined by the method of Wenger, Cimerman and Rzymowska.<sup>18</sup> Calcium and phosphorus were estimated by the methods of Clark and Collip<sup>4</sup> and of Fiske and Subbarow,<sup>6</sup> respectively. McGeorge's modification<sup>11</sup> of the procedure of Stedman, Stedman and White was used for the determination of the activity of serum choline esterase.

When the observations were begun, the serum calcium was 10.7 mg. per 100 cc., phosphorus 3.0 mg. per 100 cc. and esterase activity 2.31 cc. of N/100 sodium hydroxide, that is to say within



the normal range (Table 1). The serum potassium, however, was 11 mg. per 100 cc., only 50% of normal level. The administration of the 2 doses of potassium chloride of 4.2 gm. each, effected no significant immediate change in the serum potassium (Table 1). When recovery was complete, however, it was 25.3 mg. per 100 cc., in the normal range. The calcium, phosphorus and serum esterase remained normal.

TABLE 1.—THE RELATIONSHIP OF ELECTROCARDIOGRAPHIC CHANGES TO CHEMICAL ALTERATIONS OF THE BLOOD SERUM IN PERIODIC FAMILIAL PARALYSIS.

EKG	Date.	Time.	Cardiac rate, per min.	P-R <sub>2</sub> sec.	QRS <sub>2</sub> sec.	Q-T <sub>2</sub> sec.	Serum potassium, mg. per 100 cc.	Serum phosphorus, mg. per 100 cc.	Serum calcium, mg. per 100 cc.	Serum esterase, cc. N/100 NaOH
A	1936 2/14	11.35 A.M.	86	0.14	0.10	0.32				
	2/21	....	..	..	..	..	..	5.20	11.4	
B	1939 6/18	9.00 P.M.	100	0.24+	0.20	0.36+	11.0	3.00	10.7	2.31
	6/18	9.50 P.M.	—	Potassium chloride 4.2 g.	m. by mouth	h—				
C	6/18	11.15 P.M.	83	0.24+	0.12	0.44+	11.0	2.92	..	2.26
	6/18	11.40 P.M.	—	Potassium chloride 4.2 g.	m. by mouth	h—				
D	6/19	1.20 A.M.	94	0.22+	0.11	0.40+	12.1	3.04	..	2.32
E	6/19	9.00 A.M.	97	0.16	0.09	0.32	25.3	4.00	11.1	2.22
F	10/24	10.15 A.M.	86	0.14	0.10	0.32	18.0	4.80	11.7	2.52

During the patient's first admission in 1936, the electrocardiogram was essentially normal in its configuration (Fig. 1A). The rhythm was regular, the rate 86 per minute, the P-R<sub>2</sub> conduction time measured 0.14 second, the Q-T interval 0.32 second; the QRS<sub>2</sub> time was at the upper limit of normal (0.10 second) (Table 1). The first electrocardiogram (Fig. 1B), taken during the paralysis, showed a bizarre form. Normal sinus rhythm persisted, the rate now 100 per minute. It was not possible to measure the P-R<sub>2</sub> time, because the auricular complex could not be isolated from the positive wave following the R wave; later records established this as the T wave. It was likely that the P wave in this record was buried in this deflection for throughout the series the origin of the impulse is in the sinus node. Nor could the QRS time be measured accurately because of the deep, split S waves which occurred in all leads. Likewise there was deformity of the R-T segments. However, from the isoelectric level before the R wave to the isoelectric level following it, the duration was, at least, 0.24 second. It was not possible to measure the Q-T interval accurately, but it was more than 0.36 second. This

A. N. No. 121246 Age 19 yrs. ♂

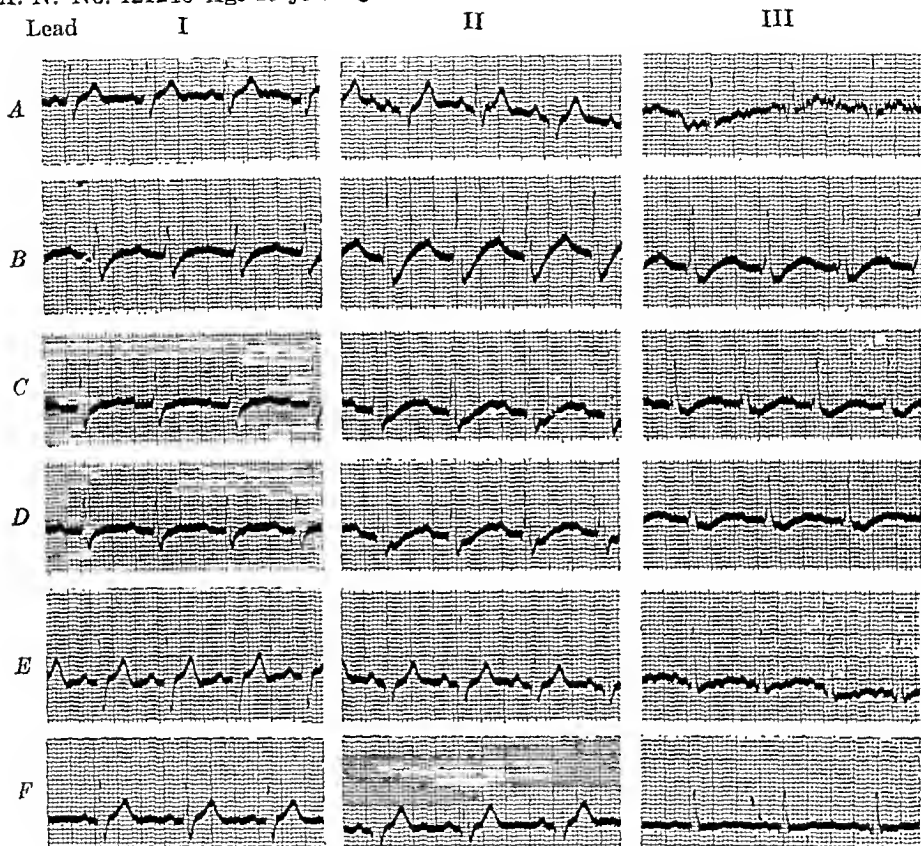


FIG. 1.—FIG. 1A, which serves as a control, was taken on February 14, 1936; FIG. 1B, on June 18, 1939, during an attack of paralysis; FIG. 1C, 85 minutes after the administration of the first dose of 4.2 gm. of potassium chloride; FIG. 1D was recorded 110 minutes after the second dose of 4.2 gm. of potassium chloride; FIG. 1E was taken after the attack had terminated on the morning of June 19, 1939; FIG. 1F, taken on October 24, 1939, approximately 4 months after discharge, serves as an additional control. The 3 standard leads were recorded. Divisions of the ordinates equal  $10^{-4}$  volts; divisions of the abscissæ equal 0.04 second.



record did not have the configuration characteristic of bundle branch block; there was obviously, however, delay in the spread of the excitation wave. The serum potassium at this time was 11 mg. per 100 cc.

Potassium chloride was given in 2 doses of 4.2 gm. each and as the patient improved in the ability to move his muscles the electrocardiogram underwent certain significant changes although the potassium concentration in the serum was not altered (Table 1). In the record (Fig. 1C) taken 100 minutes after the administration of the first dose of potassium, the heart rate was slightly lower. *P* waves were identified on the downward limb of the *T* waves. It was possible to approximate the *P-R<sub>2</sub>* time, which was prolonged and occupied, at least, 0.24 second. The *T* waves were of approximately the same height and configuration as in the previous record (Fig. 1B). The duration of electrical systole was now 0.44+ second. The level of the serum potassium remained 11 mg. per 100 cc.

The patient was given a second dose of potassium chloride 4.2 gm. The next electrocardiogram (Fig. 1D) showed progression of the changes that were already apparent in the preceding electrocardiogram (Fig. 1C); the serum potassium was, however, only 12.1 mg. per 100 cc. The *P* wave was now more easily detected and the *P-R* interval was 0.22+ second, the *QRS* time 0.11 second, the *Q-T* interval 0.40+ second. The next morning, a few hours after the dramatic clinical improvement with recovery from paralysis, the electrocardiogram (Fig. 1E) was in all major respects similar to the one recorded 3 years earlier (Fig. 1A). The *P-R* conduction time was within normal limits, the *QRS* time remained at the upper limits of normal; the *Q-T* time was now 0.32 second. The serum potassium at this time had risen to 25.3 mg. per 100 cc., a high normal level, while the calcium and phosphorus levels and the serum esterase activity were not altered. Studies were repeated on October 24, 1939, approximately 4 months later. During this time, the patient had suffered no major attacks of paralysis. The electrocardiogram (Fig. 1F) remained of normal configuration. The serum potassium at this time was 18 mg. per 100 cc. (Table 1). The serum calcium was 11.7 mg. per 100 cc.; the serum phosphorus was 4.8 mg. per 100 cc., just beyond the upper limits of normal.

**Discussion.** During the attack of paralysis there were certain marked changes in the form of the electrocardiograms. These were for the most part related to the *QRS-T* portions of them. There were no significant changes in the amplitude of the *R* or *S* waves. The *T* waves were of normal height and configuration in the control electrocardiograms. During the attack, when the serum potassium was low, the *T* waves were broad and low and the *R-T* segments changed in form in addition to those changes which were introduced by the superimposed *P* waves. The change in the *T* waves afforded further evidence of a reciprocal relationship between the *T* wave

and the serum potassium concentration. Winkler, Hoff and Smith<sup>19a</sup> have shown that the first effect of the injection of potassium chloride solution in animals was increase in amplitude of *T* waves and shortening their duration until they equalled the *QRS* complex in amplitude and duration. Likewise, the work of Thomson<sup>17</sup> established a direct relationship between the height of the *T* waves and serum potassium levels in Addison's disease.

The most striking changes appear to be effects on the conduction of the excitation wave. This is shown by lengthening of the *P-R* time, prolongation of the *QRS* time. Increase in *Q-T* interval was conspicuous. Barker, Johnston and Wilson<sup>3</sup> have pointed out the abnormal prolongation of the *Q-T* interval in cases of hypocalcemia. In this state, however, the changes appear to take place with prolongation of the isoelectric level between the *R* and *T* waves, while in familial periodic paralysis there are alterations in the *QRS* conduction time and in the form of the *T* waves and *R-T* segments. We attribute these changes to a modification of one of the fundamental properties of heart muscle, namely conduction, associated with the low potassium concentration in the blood serum. The general configuration of the changes in the electrocardiograms of our patient during paralysis was similar to those recorded by Janota and Weber.<sup>10</sup> In our case, however, they were more marked. Our finding that paralysis of the muscles disappeared after the oral administration of potassium chloride while the serum potassium concentration still remained low is similar to the experience of Gammon, Austin, Blithe and Reid.<sup>8</sup> In our patient, the serum potassium was low during the attack and unaltered by the administration of the salt, but was, on the other hand, at a normal level after recovery from paralysis. Electrocardiographic changes, however, occurred during the administration of the potassium chloride and as recovery progressed. The levels of calcium and the activity of serum choline esterase throughout showed no deviation from the normal. It may be significant that the value for serum phosphorus of 5.2 mg. per 100 cc. previously reported in this patient by Milhorat<sup>13</sup> in a paralysis-free interval was in the normal range. During paralysis, however, it was in the low normal range, 3.0 mg. per 100 cc., and attained a normal level of 4.8 mg. per 100 cc. after recovery. We have no explanation for this change. It may be recalled that values of the same order have been reported by Aitken, Allott, Castleden and Walker.<sup>1</sup>

**Summary and Conclusions.** The electrocardiographic changes during an attack of familial periodic paralysis have been studied together with the concentrations of serum potassium, calcium, phosphorus and serum esterase activity. These correlations have not before been reported. The most striking changes and those responsible for the bizarre form of the electrocardiogram were prolongation of the *P-R*, *QRS*, *Q-T* intervals, alteration in the form of the

*R-T* segments, and decrease in amplitude of the *T* waves. Certain of these changes were evidence of a defect in the propagation of the excitation wave. During paralysis the serum potassium was only half the value recorded after recovery from the attack, as well as 4 months later. We are of the opinion that the electrocardiographic changes are associated with the reduction in serum potassium. Certain data which have been published support this view.<sup>12,14,17,19a,b</sup>

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### THE PROGNOSTIC SIGNIFICANCE OF RIGHT AXIS DEVIATION IN ARTERIOSCLEROTIC AND HYPERTENSIVE HEART DISEASE.

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THOUGH axis deviation is not diagnostic of left or right ventricular hypertrophy in every instance, well-marked enlargement of either the left or right ventricle is commonly associated with left or right axis deviation respectively. It is therefore of interest to report a series of cases of hypertensive and arteriosclerotic heart disease, the majority of whom had left ventricular hypertrophy and in whom electrocardiograms revealed right axis deviation. The prognostic significance of this finding is discussed.

**Material.** In the electrocardiographic records of this hospital from 1929 through 1938, right axis deviation was found in 36 cases of hypertensive or arteriosclerotic heart disease. Right axis deviation was regarded as present when *S* 1 was greater than *R* 1, which was often small or absent, and when *R* 3 was equal to or greater than *R* 2. In the majority of cases the angle was above  $+80^\circ$  or the

index more than  $-10$ . In a few cases the axis was within the high limits of normal, but a definite tendency to right axis deviation was present. Cases of rheumatic heart disease, congenital heart disease and right ventricular hypertrophy due to chronic pulmonary disease were excluded. There were 27 male and 9 female patients in this group ranging from 32 to 75 years of age. Twenty-one had blood pressure levels above 160 mm. systolic, and 100 diastolic. Recent attacks of coronary thrombosis had occurred in 12 of these 21 according to their histories, to objective evidence, or both; attacks of coronary thrombosis had also occurred in 14 of the remaining 15 non-hypertensive cases. One patient had luetic aortitis with an aortic aneurysm (Case 29, Table 1). Of these patients, 24 have died and postmortem examination was performed in 13; 5 patients are still alive and 7 have not been traced (Table 1).

TABLE 1.

No.	Age. Sex.	Hyper- tension.	Clinical cor. thromb.	Con- gestive failure.	Cardiac enlargement.		Time of ap- pearance of rt. ax. dev. after cor. thromb.	Duration of life after appearance of rt. ax. dev.
					Clinical.	X-ray.		
1	32 M	0	+	0	0	..	2 weeks	Alive, 4 months
2	36 M	0	+	0	0	0	1 month	Alive, 21 months
3	46 F*	+	+	+	+	+	9 weeks	Alive, 13 months
4	52 M*	0(?)	+	+	0	0	8 months	Alive, 32 months
5	55 M†	0	+	+	0	..	3 days	Alive, 11 months
6	45 F	+	+	0	+	..	3 days	Died, 1 day
7	45 M	0	+	0	0	..	3 days	Died, 2 weeks
8	45 M	+	0	+	+	..	....	Died, 17 days
9	48 M	0	+	0	+	..	1 week	Died, 12 days
10	52 M	0	+	+	0	..	24 days	Died, 18 months
11	52 F	+	0	+	+	..	....	Died, 10 months
12	55 F	+	0	+	+	..	....	Died, 18 days
13	58 M	0	+	+	+	+	12 months	Died, 1 month
14	59 M	+	0	+	+	+	....	Died, 3 days
15	59 F	+	0	+	+	..	....	Died, 5 months
16	61 M	+	+	+	+	..	2 months	Died, 2 months
17	62 M	0	+	+	+	..	1 day	Died, 9 days
18	63 M	+	+	+	+	+	6 months	Died, 5 weeks
19	63 M	+	+	+	+	..	1 day	Died, 6 days
20	63 M	0	+	+	+	0	2 weeks	Died, 8 days
21	64 M	+	+	0	+	..	4 days	Died, 2 days
22	65 M	0	+	0	0	0	2 weeks	Died, 15 months
23	65 M	0	+	+	+	+	2 months	Died, 27 months
24	67 F	+	0	+	+	..	....	Died, 4 months
25	61 M	+	+	+	0	..	?	Died, 6 months
26	71 M	+	0	+	+	..	....	Died, 1 week
27	74 M	+	+	+	+	+	3 months	Died, 2 days
28	75 M	+	+	+	0	..	4 months	Died, 2 weeks
29	45 M	0	0	0	+	+	....	Untraced
30	54 F	+	0	+	+	+	....	Untraced
31	55 M	+	+	+	+	+	11 months	Untraced
32	57 F	+	+	+	+	..	?	Untraced
33	61 M	0	+	+	+	..	3 days	Untraced
34	61 F	+	0	0	+	0	....	Untraced
35	63 M	0	+	0	+	..	5 weeks	Untraced
36	46 M	+	+	+	+	..	5 days	Died, 8 days

\* Markedly diminished cardiac reserve.

† Bedridden.

Nine patients had electrocardiograms taken prior to the development of right axis deviation; in 7 the axis was normal and in 2 left axis deviation was present. In 7 cases of the total group of 36 the occurrence of the right axis deviation was temporary, changing within a few days to a few months to normal axis or to left axis deviation. Enlargement of the heart to the left was found by clinical examination, by Roentgen ray study, or by both, in 27 of the 36 cases. Left ventricular hypertrophy was present in all 13 autopsied cases. Right ventricular hypertrophy was also found in 4 cases, but in each of these the left ventricle was hypertrophied to an even greater degree. All the patients studied at postmortem showed definite left ventricular preponderance. The heart weighed more than 500 gm. in 8 and less than 400 gm. in only one case (Table 2). Severe coronary disease was present in 12 of the autopsied cases, with occlusions of one or more of the major coronary arteries in 11. Myocardial infarcts were found in 10, 8 of them of recent origin. In 3 cases the infarct was wholly anterior, in 3 it was anterior and septal, in 1 other the infarcts were both anterior and posterior, while in the remaining 3 cases they were posterior. In 2 of the 3 cases without myocardial infarction diffuse fibrosis was present. In the autopsied cases in which myocardial infarcts were found, the areas of myocardial necrosis were extensive.

**Report of Autopsied Cases (Table 2).** CASE 1.—M. K., a 45-year-old female diabetic with hypertension, had a normal electrocardiogram 2 years prior to admission. Two days before entry she experienced a sudden seizure of severe precordial pain with collapse. Electrocardiograms the first 2 days disclosed normal axis, inversion of *T* 1, and depression of *ST* 2 and *ST* 3. On the third day right axis deviation appeared. The *QRS* complexes were slurred and were 0.10 second in duration. The patient died on the fourth hospital day.

CASE 2.—S. L., a 45-year-old male with a questionable history of hypertension had an attack of severe precordial pain one year before admission persisting for 2 days. The day before admission a more severe attack occurred. An electrocardiogram on the second day disclosed normal rhythm, right axis deviation, elevated *ST* segment with coronary type inversion of *T* 1, absent *Q* 4 and deeply depressed *ST* 4 (old method). The *QRS* complexes were notched and were 0.12 second in duration. During the next few days the axis gradually changed until, on the 15th day, left axis deviation was present. The patient died on the 16th hospital day.

CASE 3.—I. B., a 45-year-old male with hypertensive heart disease, was admitted in congestive heart failure with a history of increasingly severe angina pectoris and paroxysmal dyspnea. An electrocardiogram on the 4th hospital day revealed normal rhythm, a tendency to right axis deviation and inverted *T* 2 and *T* 3. The *QRS* waves were normal. The patient died 21 days after admission.

CASE 4.—J. S., a 48-year-old male with a history of angina pectoris was admitted 5 days after a particularly severe episode of pain. An electrocardiogram the day after admission showed normal rhythm, right axis deviation, deep *Q* 2 and *Q* 3, inverted *T* 3 and absent *Q* 4 (old method). The *QRS* complexes were slurred and notched but were only 0.10 second in duration. He gradually failed and died 2 weeks after admission.



TABLE 2.—DATA IN AUTOPSIED CASES.

No.	Age. Sex.	Hypertension.	Clin. cor. thromb.	Congest. failure.	Degree coronary disease.	Heart weight.	Coronary vessels occluded or narrowed.			Cardiac infarcts.		Hydrothorax (in cc.).	
							L.A.D.	L.C.	R.C.	Old.	Recent.	Right.	Left.
1	45 M	+	+	0	3	410	+	0	0	0	+	0	0
2	45 M	0	+	0	3	360	+	0	+	0	+	1400	1000
3	45 M	+	0	+	3	650	+	+	0	+	0	750	700
4	48 M	0	+	0	3	440	+	+	+	0	+	150	0
5	58 M	0	+	+	3	530	0	0	+	+	0	50	1000
6	59 M	+	0	+	3	1000	N	N	N	*	*	0	0
7	63 M	+	+	+	2	640	0	0	0	0	0	250	0
8	63 M	+	+	0	3	410	N	+	+	0	+	++	++
9	64 M	+	+	+	3	580	+	0	0	0	+	500	500
10	71 M	+	0	+	3	740	0	0	+	*	*	0	0
11	74 M	+	+	+	3	600	+	+	0	0	+	250	250
12	75 M	+	+	+	3	490	+	0	+	0	+	250	250
13	46 M	+	+	+	3	520	+	0	0	0	+	0	0

3 = Marked coronary disease—marked narrowing or occlusion of major vessels.

2 = Moderate coronary disease—diffuse atherosclerosis without narrowing of major vessels.

\* = Diffuse fibrosis.

L.A.D. = Left anterior descending branch.

L.C. = Left coronary.

R.C. = Right coronary.

CASE 5.—J. E., a 58-year-old male with no history of hypertension or cardio-respiratory symptoms, was admitted with severe substernal pain of 1 day's duration. An electrocardiogram on admission disclosed normal rhythm, left axis deviation, elevated *ST* 2 and *ST* 3 and inverted *T* 2 and *T* 3. The patient improved and was discharged on the 20th hospital day. One year later he was readmitted in congestive failure, and the electrocardiogram now showed normal rhythm, right axis deviation, inverted *T* 2 and *T* 3 and normal *QRS* complexes. He became progressively worse and died one month after admission.

CASE 6.—D. G., a 59-year-old male with hypertensive heart disease and a history of congestive heart failure and angina pectoris of several years' duration, was admitted in severe congestive failure. Electrocardiogram on the 4th day showed auricular fibrillation, normal axis, inverted *T* 1 and flat *T* 2, a deep *S* 2 and upright *T* 4 (old method). The patient was discharged improved after 3 weeks. Three months later he was readmitted in congestive failure with similar electrocardiographic findings and was discharged improved after 2 weeks. One year after the second admission he was readmitted in congestive failure, and died on the 5th hospital day. Electrocardiograms taken on the 2d, 4th, and 5th hospital days showed auricular fibrillation and a progressively increasing tendency to right axis deviation. The *QRS* complexes were normal in duration and shape.

CASE 7.—C. B., a 63-year-old male with hypertensive heart disease and a history of angina pectoris, paroxysmal dyspnea and congestive failure, was admitted in severe failure. One year, and again 8 months before admission he experienced crushing precordial pain, marked dyspnea and weakness requiring bed rest. Electrocardiograms on the 4th, 12th and 19th hospital

days revealed normal rhythm, right axis deviation, delayed A-V conduction, diphasic *T* waves and notched *QRS* waves of 0.08 duration. On the 34th day the axis was normal. The patient died a week later.

CASE 8.—L. O., a 63-year-old male with a history of hypertension and angina pectoris, was admitted with recurrent attacks of more severe precordial pain. The chest pain became worse in the hospital and was accompanied by fall in blood pressure, glycosuria, dyspnea and nitrogen retention. An electrocardiogram on admission revealed normal rhythm, right axis deviation, normal Lead 4, a deep *S* 2 and slurring of the *QRS* complexes with a duration of 0.12 second. The right axis deviation persisted until the death of the patient on the 6th hospital day.

CASE 9.—J. M., a 64-year-old male with a history of hypertension and angina pectoris of 15 years' duration, was admitted in shock and congestive failure 4 days after the onset of a severe attack of substernal pain. Electrocardiograms on the first and second hospital days revealed ventricular premature beats producing trigeminy, right axis deviation, delayed A-V conduction, depressed *ST* 1 and *ST* 4, elevated *ST* 3 and inverted *T* 1 and *T* 3. The *QRS* waves were slurred and notched and 0.10 second in duration. He died on the second hospital day.

CASE 10.—A. Z., a 71-year-old male with hypertensive heart disease and a history of attacks of paroxysmal dyspnea and auricular fibrillation of 2 years' duration, was admitted in congestive failure. An electrocardiogram the day after admission revealed auricular fibrillation, right axis deviation, inverted *T* 2 and *T* 3, normal *QRS* complexes, and a normal Lead 4. The patient died on the 8th hospital day.

CASE 11.—N. L., a 74-year-old male with hypertensive heart disease, a history of angina pectoris for many years, paroxysmal dyspnea and repeated bouts of congestive failure for 4 years, was admitted in severe congestive failure. On admission the electrocardiogram showed normal rhythm, right axis deviation, delayed A-V conduction, flat *T* waves and an absent *Q* 4 (old method). The *QRS* complexes were normal in shape but were prolonged to 0.12 second in duration. The patient died on the 3d hospital day.

CASE 12.—S. G., a 75-year-old male with hypertensive heart disease and a history of coronary thrombosis 4 months prior to admission, was admitted in congestive failure. Electrocardiograms on the 2d and 3d days after admission showed normal rhythm, normal axis, depressed *ST* 1 and *ST* 2, inverted *T* 3 and deep *Q* 3 wave and normal Lead 4. On the 6th hospital day right axis deviation appeared. The *QRS* complexes were normal. The patient died on the 19th hospital day.

CASE 13.—A. H., a 46-year-old male with a past history of tuberculosis, subacute glomerulonephritis and hypertension was admitted with severe left anterior chest pain of 2 days' duration. An electrocardiogram on the 2d hospital day revealed sinoauricular tachycardia, right axis deviation, elevated *ST* 1, 2, and 4, depressed *ST* 3 and inverted *T* 1. The right axis deviation persisted until death. The patient died on the 10th hospital day.

**Discussion.** Einthoven<sup>5</sup> and Lewis<sup>7a</sup> believed that well-marked deviation usually indicated hypertrophy of the corresponding ventricle. White and Bock<sup>12</sup> and White and Burwell<sup>13</sup> concluded that diseases predisposing to right or left sided hypertrophy caused right or left axis deviation respectively. There were, however, small groups of cases in which there was no correspondence between the axis deviation and ventricular preponderance; to explain these Pardee<sup>9</sup> suggested a relationship between axis deviation and the

position of the heart in the chest. Herrmann and Wilson<sup>6</sup> believed that disturbances of atrioventricular conduction might cause changes in axis deviation. The electrical axis of the heart, according to the above authors, is therefore dependent on the position of the heart in the chest, the type of atrioventricular conduction and the relative weights of the two ventricles.

The data presented here further emphasize the discrepancies between electrical axis and ventricular preponderance especially since the right axis deviation is considered to be associated rather constantly with right ventricular preponderance.<sup>10</sup> Twenty-one of these patients had hypertension which commonly presents left ventricular preponderance and left axis deviation. Furthermore, in 13 cases the axis changed one or more times under observation. Bundle branch block, which is known to cause variations in axis deviation, was not present in any of these cases, although in 9 instances the *QRS* complex was slurred and notched and prolonged to 0.12 second, suggesting an intraventricular conduction defect (Table 3). Hydrothorax was present in 14 patients, but in only 5 cases was it limited solely to the left pleural cavity. Lewis states, furthermore, that "displacement by pleural effusion does not appear materially to influence the electrocardiogram."<sup>7b</sup>

TABLE 3.—ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH  
RIGHT AXIS DEVIATION.

Type.	Cases.	%.
Delayed A-V conduction . . . . .	6	17.1
Intraventricular block . . . . .	9	25.7
Auricular fibrillation . . . . .	6	17.1
Inverted <i>T</i> 1 . . . . .	12	33.3
Inverted <i>T</i> 2 and <i>T</i> 3 . . . . .	10	28.6
Inverted <i>T</i> 3 . . . . .	3	8.6
Abnormal <i>ST</i> segments . . . . .	12	33.3
Deep <i>Q</i> 3 . . . . .	6	17.1
Absent <i>Q</i> 4 or <i>R</i> 4 . . . . .	11	31.4
Deep <i>S</i> 2 . . . . .	5	14.3

The presence of right axis deviation in hypertensive and arteriosclerotic heart disease has received scant attention. Nathanson<sup>8</sup> found slight right axis deviation in 2 cases (3.3%), in a group of 60 with advanced coronary disease. Isolated instances of right axis deviation have been noted by other workers in cases of coronary occlusion.<sup>1</sup> Bohning and Katz<sup>2</sup> found that "right axis shift" was infrequent in coronary occlusion, occurring only in some cases of anterior infarction. Comeau and White<sup>3</sup> in a recent publication found coronary disease in only 7 of 200 cases of right axis deviation (3.5%) and concluded that this abnormality was very uncommon in coronary sclerosis. The present study indicates that right axis deviation such as occurs in hypertensive and arteriosclerotic heart disease is commonly associated with the syndrome of coronary

thrombosis. The pathologic findings in the 13 autopsied cases and the clinical findings in the rest suggest that the underlying lesions in all instances were left ventricular hypertrophy, severe coronary disease and extensive myocardial damage. Right axis deviation is associated with electrocardiographic changes suggestive of anterior infarction (inverted  $T$  1 and  $T$  2, absent  $Q$  4), as commonly as electrocardiographic changes indicative of posterior infarction (inverted  $T$  2 and  $T$  3, deep  $Q$  3) (Table 3). The postmortem findings also show that the locations of the infarcts in such cases is not characteristic.

The mechanism of this abnormal and unusual change in the electrical axis is obscure. The  $QRS$  complex is regarded as representing the spread of the excitation waves throughout the ventricles, recording only electrical phenomena. These are dependent on the health of the ventricular musculature and conduction system. Abnormal deviations of the electrical axis are believed to be associated with preponderant disease of one ventricle, and the most common cause of axis deviation is disproportionate hypertrophy of one ventricle. It is evident from the present study that another mechanism causing changes in the electrical axis of the heart is widespread necrosis of one ventricle, which can so interfere with the conduction system of the myocardium as to completely nullify the effects of hypertrophy.

It is significant that 83% of the patients in whom follow-up studies were made died within 27 months after the development of right axis deviation; 43% of the total series died within 1 month. Conner and Holt<sup>4</sup> found an immediate mortality of 16.2% in their analysis of 287 patients with coronary thrombosis. White and Bland,<sup>11</sup> found that the average duration of life after an attack of coronary thrombosis was 2.4 years in a group of 200 cases. The present study indicates that there is a higher initial mortality and that the average duration of life after the attack is only 7.6 months in patients who show right axis deviation after coronary thrombosis. The presence of right axis deviation in a patient with clinical evidences of coronary thrombosis is therefore a serious prognostic sign.

**Summary and Conclusions.** 1. Right axis deviation may occur in hypertensive and arteriosclerotic heart disease, even in the presence of left ventricular hypertrophy.

2. It is commonly associated with recent attacks of coronary thrombosis and with severe myocardial damage. In 13 autopsied cases myocardial infarcts were found in 10 and diffuse fibrosis in 2. Right axis deviation occurs in cases with anterior or posterior infarction singly or in combination.

3. Of the patients with right axis deviation in whom follow-up studies were made, 83% died within 27 months and 43% of the total series died within 1 month of its discovery. The occurrence of right axis deviation in patients with hypertensive or arteriosclerotic

heart disease without rheumatic and congenital heart disease or cor pulmonale indicates a poor prognosis.

4. Another mechanism altering the electrical axis of the heart may be widespread necrosis of one ventricle which can completely nullify the effects of hypertrophy of that ventricle.

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### THE TREATMENT OF ALCOHOLISM BY ESTABLISHING A CONDITIONED REFLEX.

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THE utilization of the principle of the conditioned reflex in the treatment of alcoholism was first suggested by Markovnikov<sup>4</sup> and by Ichok,<sup>3</sup> in 1934. The former author cited some experimental results, but Ichok presented only a philosophic discussion of the subject.

A conditioned reflex may be defined as the eliciting of a normal or unconditioned reflex response by means of a strange or unnatural stimulus. Thus if salivation in an experimental animal is made to result solely from the stimulus of a ringing bell, a conditioned reflex has been established. These reflexes are called conditioned reflexes because they require a period of training or conditioning before they may become manifest. The fundamental concept of the conditioned reflex and the importance of its several peculiar characteristics has been studied most exhaustively by Pavlov.<sup>5</sup>

**Method of Treatment.** In applying the foregoing physiologic considerations to the treatment of alcoholism, the action of certain nauseant drugs is utilized to elicit the unconditioned reflex of nausea and vomiting. The sight, smell and taste of alcoholic beverages serve as the conditioned stimulus, and thus, a conditioned reflex can be established. The physical properties of alcoholic beverages when utilized as the conditioned stimulus will, upon exhibition, initiate reflex activity of the centers of nausea and vomiting. A distaste is thus created for the conditioned stimulus, amounting to a strong and definite aversion to the sight, smell and taste of liquor. It is interesting to note in passing that an analogous con-

ditioned reflex occurs spontaneously in nature in certain cases of food poisoning. It is probable that every one after partaking of certain foods too abundantly or of "tainted" food, has experienced nausea and vomiting. It is true that after such an unfortunate experience there is left in the mind of the person an aversion or distaste, that may last for years, for the particular food in question. It is of further interest to observe that the person may experience no distaste whatever for the food actually causing the illness should it escape his suspicion. His dislike may center upon an entirely blameless and innocent food that was eaten just prior to his illness. This observation indicates the importance of suggestion in establishing the conditioned reflex.

The establishment of a conditioned reflex aversion to alcohol is undertaken during a number (usually 5 to 7) of seances or treatments with rest periods between. The average hospital stay is 5 days. No food except liquids and no sedative drugs are given for at least 12 hours prior to each treatment. Our choice of nauseant drugs lies between emetine and apomorphine. We have chosen emetine because its action is more prolonged and it produces no hypnotic effect following its use to complicate the interpretation of the results. However, small doses of apomorphine given in conjunction with the emetine achieve a degree of nausea and emesis impossible with emetine alone. Each treatment should be given only by a physician especially trained and experienced in this work. Experience has taught that a certain hazard exists in the administration of the treatments. Alarming though not dangerous collapse may follow the injudicious administration of the suggested medication.

The treatment room is constructed with special attention given to the physical comfort of the patient during treatment. The room is soundproofed in order to avoid extraneous stimuli, such as conversation, street noises and all other distracting influences. The lighting is subdued with the exception of the treatment table. It is believed worth while to have the treatment table with its array of liquors "spot lighted" in plain view. The patient's attention is thereby constantly focused on our conditioned stimulus. This attention to the visual sense will cause the sight of liquor to become one element of our conditioned stimulus. Similarly, by forcing the patient to smell deeply of various liquors at every possible opportunity during the treatment, the olfactory sense may also be utilized as still another element of the conditioned stimulus. These points are of vital importance. In our experience we have found aversion to the sight and smell of liquor to be very marked following completion of the course of treatments. Usually this aversion to sight and smell is sufficient to cause the patient to avoid alcohol without the more dangerous experiment of tasting liquor that he may satisfy his curiosity relative to his inability to drink.

Since the conditioned stimulus is specific, it is necessary to use every conceivable type of liquor as our conditioned stimulus. However, the particular type of beverage usually consumed should receive the greatest stress. If this technique were not observed it would be possible to create a successful aversion to whiskey, for example, and none to other liquors or beer.

The drugs used during the treatment are made up in 40 cc. ampules from which individual doses may be drawn with ease and accuracy. The proportions used are as follows:

Emetine HCl . . . .	50 grains	Ephedrine SO <sub>4</sub> . . . .	23 grains
Pilocarpine . . . .	25 grains	Water . . . .	qs 40 cc.

Pilocarpine is included not only because of the psychic effect of its producing profuse diaphoresis and sialorrhea, but also because of the feeling among older writers that it helps combat the physical taste for liquor. The ephedrine is used to combat the fall in blood pressure experienced by some patients after emetine administration. We feel that a fall in systolic blood pressure below 100 is indication for rest and continued ephedrine medication until a near normal level is again reached.

In administering the actual treatment the following routine is used. The patient is made comfortable in the treatment room and the appropriate dose of the emetine-pilocarpine-ephedrine mixture is given (Minims vi to xii) hypodermically. Variations in dosage depend not so much on body weight as upon the personality of the patient. Selection of the proper amount is largely based on previous experience and observation of the effect obtained during the first treatment. It is well to mention casually to the patient that this medication is merely a stimulant to support him during the ensuing violent nausea. Such a remark serves not only to remove the injection as a possible source of the following nausea but also suggests to the patient that the drinking of the liquor is going to make him acutely ill. Experience alone will enable one to judge the exact moment when the emetine nausea will begin (usually 2 to 8 minutes) and consequently the exact moment when the first drink of liquor should be offered. It is of paramount importance that this first offering of liquor should be given within several seconds before the onset of nausea and certainly under no conditions should it be withheld until either nausea or salivation has appeared. An error of only a few seconds in the first admission of alcohol will not only annul the effect of the treatment but will, according to our experience, make the patient recalcitrant to further efforts to establish a satisfactory conditioned reflex. If an error in timing has been committed and the liquor is given prematurely the onset of nausea may be hastened by administering 1 to 2 grains of emetine orally in whiskey. Since this drug apparently acts centrally to lower the threshold of mucosal irritability the effect after oral adminis-

tration at this time is more quickly manifest than would be an additional hypodermic injection. Since this oral intake of emetine is almost entirely rejected before absorption can take place one can disregard the effect of this administration from a systemic point of view. Following the onset of nausea all types of liquor are forced on the patient, making certain that each empty glass is smelled deeply. Warm water is given frequently in order to afford easy emesis and to avoid retching. After emesis is completed the above routine is repeated until the nauseant effect has begun to wane. The stomach is then thoroughly emptied and washed with warm water using the Ewald tube. The patient is then covered carefully and left in the treatment room until the pilocarpine diaphoresis has ceased.

Occasionally a patient is unable to regurgitate in spite of deep nausea. In these instances the stomach must be emptied promptly via the Ewald tube. Absorption of alcohol to the point where an effect is noted by the patient will vitiate the entire treatment. The necessary use of the Ewald tube does not in any way render the treatment less effective.

It has been found that an occasional patient develops little or no nausea following the administration of emetine. In these cases it has been noted that the hypodermic injection of a small dose of apomorphine (grains  $1/20$  to  $1/40$ ) in conjunction with emetine will invariably initiate severe nausea. This procedure must be used with much caution due to the fact that approximately 30% of the patients so treated develop alarming syncope coupled with marked bradycardia amounting in a few instances to complete momentary cardiac standstill coincident with the onset of nausea. This is of course on the basis of strong vagus stimulation of central origin and may be overcome largely with preliminary atropine medication. Pilocarpine should not be given when the mixed treatment with emetine and apomorphine is used.

Routine laboratory work was performed on each patient, including daily chemical and microscopic urinalysis, blood pressure determinations 3 to 5 times daily, as well as the indicated blood-chemistry studies.

Contraindications to the treatment comprise in the main the cardio-vascular-renal syndrome, hepatic cirrhosis with or without esophageal varices, hernia (unless guarded), active peptic ulcer or history of recent hematemesis and active psychosis.

**Results.** In the past 4 years 685 patients with chronic alcoholism have been treated by the foregoing method. Of this total number the exact status of 538 of these patients is known. The latter figure will form the basis of the statistical data to be presented.

The answer to the question as to results is of course based on the percentage of cures obtained. Chart 1 shows graphically the percentage of complete abstinence among patients treated during each



6-month period for the past 4 years. Examination of these data will reveal that with the exception of the most recent and the most remote periods, the percentage of sobriety is remarkably constant, varying only between 62 and 69%. It is felt that the low percentage (50%) noted in the most remote period (48 months) is due to the fact that this group represents the first cases treated more or less experimentally and that certain mistakes and omissions of technique occurred, which have later proven to be most important, and that a relatively poor result was thereby obtained. While the percentage

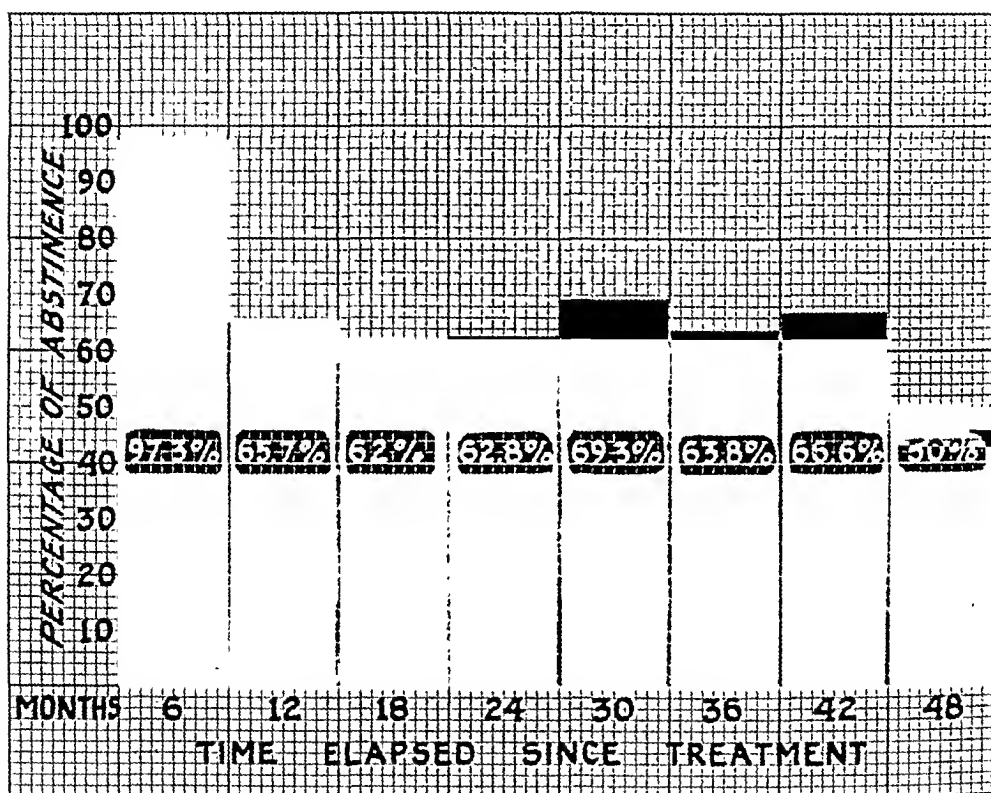


CHART 1.—Showing the percentage of abstinence at the present time among patients treated during each 6-month period during the past 4 years.

of abstinence for the 6-month period immediately following treatment is found to be 97.3%, the percentage during the second 6-month period is seen to be only 65.7%. This indicates clearly, in view of the number of cases reported, that the great majority of relapses occurred between the sixth and twelfth months following treatment. It is believed in view of these figures that if a relapse does not occur during the first year, the subsequent danger of a relapse is not great. The slight fluctuations shown after the first year in the graphic representation of the data are due to variations

in personality types vagariously included in any particular period with a corresponding tendency to make the results of that period better or worse, as the case may be. It would be illogical to consider these variations as a function of the factor of elapsed time following treatment. By obtaining an average figure for all of the 6-month periods after the end of the first 6 months, and even including the remote period of experimentation, it would seem from the data presented that by this method we have a conservative expectation of 64.3% of total and permanent cures. By a "cure" in this sense is meant total and permanent abstinence from alcohol of all types.

The average age of admission was 41.5 years. The average age of those returning to drink was 38.0 years, showing the tendency for younger patients to relapse. It is interesting to note that among the entire series of cases we have been unsuccessful in treating a single individual under 28 years of age. The percentage of abstinence among women patients was found to be 57% following treatment, which is somewhat below the average for the entire series. No correlation was found to exist between relapses and either duration or severity of addiction. Relapses are more common, however, among wine drinkers than beer drinkers and least frequent among patients who are users of distilled liquors such as whiskey.

Many of the patients who have returned to drinking following treatment have presented themselves for retreatment. While we have as yet no authoritative data to report in this connection, it is indicated from experience that the prognosis in these cases is poorer than in the untreated group. Many of these patients have relapsed a second time soon after treatment.

Considering the fact that the majority of patients presenting themselves for an alcoholic cure are confirmed and heavy drinkers and that they usually come during a prolonged spree, and considering, further, that alcohol is withdrawn suddenly during treatment, it is surprising that delirium tremens developed in only 14 (2%) of the total number of treated cases. Twenty-one patients were admitted in acute delirium. We have felt in the past that our freedom from delirium was due to the spontaneous dehydration<sup>2</sup> of the patient following profuse pilocarpine diaphoresis and emesis. Chart 2 showing the average of 100 unselected cases indicates the extent of dehydration in spite of the fact that fluids are forced during the treatment. That the sedative action of alcohol on the central nervous system is not the sole factor as suggested by Tatum<sup>8</sup> is indicated by the fact that only rarely is it necessary to administer sedative medication. Recent advice, however,<sup>1,6</sup> would indicate that dehydration *per se* is not the factor that controls the incidence of delirium tremens. The further investigation of pilocarpine in the therapy of delirium is indicated. The mortality in our series of 35 cases of delirium tremens was a single case that expired before

treatment could be instituted. This represents a mortality of 2.8%, if this untreated case is included.

The mortality of the entire series of cases receiving the complete treatment was a single death (0.14%) due to cardiac failure.

Laboratory studies show that while 36.8% of patients on admission show albuminuria only 3.9% have this finding upon being discharged.

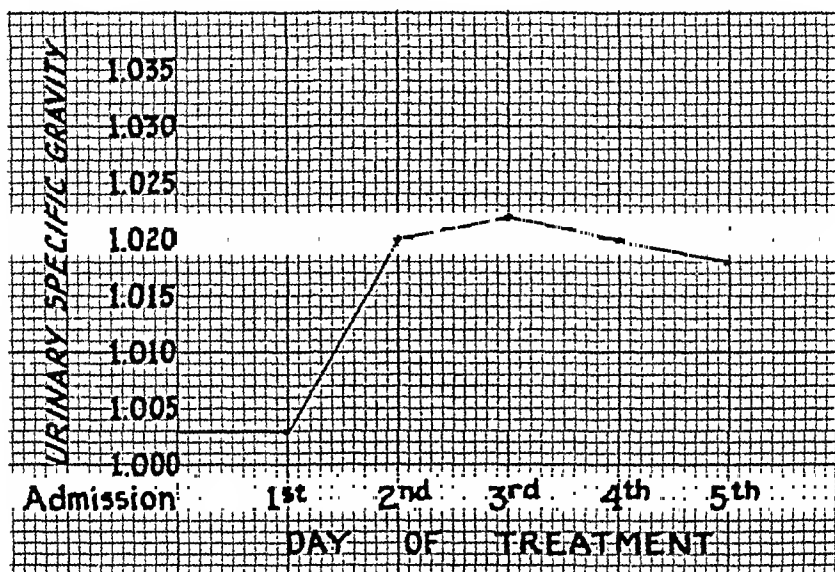


CHART 2.—Showing the increase in urinary specific gravity (dehydration) in 100 unselected cases during treatment.

**Discussion.** Failures under this method of treatment are due in very few instances to the inability to establish a satisfactory conditioned reflex. The greater proportion of failures are due to the natural breaking down and weakening of the conditioned reflex due to the lack of periodic reënforcement. This is indicated by the fact that the relapses occur during the sixth to twelfth months when the reflex might be expected to weaken or disappear. Relapses occurring before the sixth month are almost without exception characterized by gross psychopathic traits. Those cases of permanent cure are seen in individuals who possess sufficient residual psychic balance spontaneously and automatically to repair the fundamental personality defect which is the basis of their drinking during the period of enforced abstinence before the mechanism of the conditioned reflex becomes weakened to the point where it is no longer effective. This suggests the desirability of reënforcement by secondary treatment after the sixth month following the original treatment. It is felt that this practice would greatly enhance the value of the results obtained.

In our experience there are two main causes for relapse. The first is the feeling on the part of a patient that following a variable period of abstinence without conscious effort on his part, he is now able to drink socially and in a controlled manner. Only 4 of the total number (175) of relapse cases have been able to accomplish this. The second cause is curiosity on the part of the patient as to whether liquor will actually make him ill, if it should be taken. Needless to say either experiment on the part of the patient is a most dangerous procedure and will almost certainly lead to a relapse.

A most interesting sidelight on the mechanism of the conditioned reflex is furnished by the chance observation that during the development of an aversion to alcohol a simultaneous aversion to snuff is often acquired. If the latter aversion is desired by the patient, the snuff is given only before each treatment, whereas if the patient wishes to retain the habit he is instructed to chew snuff between but not immediately before the treatment. Because of the lesser psychiatric significance of the snuff habit as compared with alcoholism, we have never in our knowledge known a patient to revert to the habit of chewing snuff even though he may revert to drinking.

The medical literature is remarkable for the paucity of statistical data relating to cures by various methods of treatment for alcoholism. The gold chloride type of treatment so popular about the turn of the century, and still practiced sporadically in some parts of the country, claimed a success of 95%. Examination of further data, however, reveals that only 55% of these patients remained sober at the end of the first year and only 10% of abstinence was noted at the end of the third year. Other data<sup>7</sup> show successful results in 61% of a series of 1100 cases. These and other data, while open to error, suggest that approximately 33.3% may be reasonably considered as permanently cured. Sajous<sup>7</sup> by employing hypnotic suggestion in 1284 cases obtained favorable results in 80%. The length of abstinence and criterion of cure were not included in the data and it is assumed that the favorable results mentioned did not necessarily constitute total and permanent abstinence.

It is not the intention of this paper to claim superiority of this method over any other or to compare the results obtained by various methods of therapy. The primary interest is to present the results of treatment obtained by a method based upon the principle of the conditioned reflex. Other methods of treatment have probably unwittingly included the principle in some phase of the treatment but have apparently never premeditatively based their immediate treatment on this factor alone.

It should be noted that no attempt at psychiatric care was made with any patients of this series. It is our opinion that if appropriate mental care could have been furnished this series of cases, our percentage of relapses would have been much smaller. We have, however, made systematic efforts through social service workers to do

rehabilitation work in those cases where it is necessary that assistance be given in such matters as regaining lost positions, smoothing out domestic incompatibilities and obtaining employment, etc. It is felt that this work is of the greatest importance in aiding the reclaimed alcoholic to find his lost position in society.

**Summary.** 1. The technique of a new physiologic approach to the problem of the treatment of alcoholism, the conditioned reflex, is given.

2. Younger individuals and women are less promising patients from the standpoint of ultimate cure than are mature men.

3. The treatment is safe; having a mortality of less than 0.15%.

4. About 64% of permanent cures may be expected as a result of this treatment when rehabilitation measures are practiced following discharge.

5. Psychotherapy and routine reënforcement after the sixth month following treatment will probably improve these results markedly.

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## STUDIES ON A PURIFIED ANTIGEN FROM BRUCELLA.\*

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CUTANEOUS hypersensitiveness to specific antigen as a test for brucella infection has been used by several authors.<sup>1,2,3b,4,6,7,10b,12,15,19,20</sup> Unfortunately, a diversity of preparations<sup>3a,8,10a,13</sup> has been used as antigens, making correlation of results difficult. We have tried to obtain a standard preparation which could be measured accurately, would be a good antigen, would be stable and could be prepared easily and with the least possible denaturization.

This has been made possible by following a modification of Seibert's method<sup>18</sup> for the preparation of P.P.D. (purified protein derivative from tuberculin). Since brucella organisms cannot be

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made to grow on synthetic media, as has been demonstrated by previous investigators,<sup>11</sup> we were unable to utilize a filtrate of the cultures as with the tuberculin products.<sup>18</sup> We started with a solution of cellular constituents of the brucella organisms and proceeded to extract and purify the protein fraction.

**Method.** Strain No. 456 National Institute of Health, Washington, D. C., was used.

Large amounts of *Brucella abortus* are grown on standard nutrient agar pH 7<sup>8</sup> in Blake bottles for 72 hours at 37° C. Approximately 5 ml. of saline with 0.5% phenol are added to each bottle and left for 30 minutes in contact with the culture, to loosen the cells. The phenolized saline containing the suspension of cells is removed from the bottles with sterile pipettes and the surface of the agar thoroughly washed with more phenolized saline. The organisms are recovered by centrifuging at high speed, and dried† in a calcium chloride desiccator until they attain a horny appearance. Then they are ground in an electric grinding apparatus to obtain a fine white powder. This fine powder is mixed with 2 liters of 0.02 N sodium carbonate and placed in the refrigerator over night. Next morning the alkaline suspension is filtered, first through a paper and then through a Berkefeld candle. To the filtrate we add 0.5% phenol, to avoid bacterial contamination during the following steps of the procedure. The filtrate is then concentrated by ultrafiltration through alundum cups impregnated with 13% gum-cotton glacial acetic solution prepared according to the method described by Seibert.<sup>18</sup> The ultrafiltration is continued until the liquid is concentrated to about 100 ml., then it is washed by passing 500 ml. of distilled water through the alundum cup filter. The concentrated colloidal solution is then filtered through a paper to eliminate any insoluble material that may have sedimented during the ultrafiltration. The protein is precipitated by mixing the colloidal solution with one-fourth its volume of a 50% freshly prepared aqueous solution of trichloroacetic acid making a final concentration of 10% acid. After standing over night in the ice box, the protein precipitate is thrown down by centrifugation. Then it is washed repeatedly by centrifugation with freshly prepared 10% trichloroacetic acid solution until the washings are colorless. The protein product is then washed with large volumes of anhydrous ether by repeated triturations and centrifugations until all the acid is removed and the precipitate is completely dehydrated. The nitrogen and polysaccharide contents of protein prepared from different batches of cell cultures vary between 1 and 2%.

The final product thus obtained fulfills our requirements, for it is of a fine consistency, light brown in color, of a fairly constant chemical composition, can be measured accurately, is stable in the dry state and constitutes a good antigen. It is not completely soluble in water, but is easily dissolved by adding a few drops of 0.1 N alkali. The solution is neutralized with 0.1 N hydrochloric acid and it remains clear. This preparation has been used in determining cutaneous hypersensitiveness among contact groups and groups from the general population of the island of Puerto Rico, where endemic abortion is prevalent and in the island of St. Thomas where endemic abortion is not known to exist. At the same time, agglutinative, complement fixation and opsonocytophagic tests were made on the same subjects.

To carry out the skin test we proceeded as follows:

The purified protein product was dissolved in saline by the method described above, so that the resulting solution would contain 0.1 mg. per cc. One-tenth cubic centimeter of the solution thus obtained (containing 0.01 mg.) was injected intracutaneously over the flexor surface of the forearm.

† Drying the organisms has been introduced as a modification to the original method to obtain a higher yield of the product.

The site of injection was examined 48 hours later. In subjects that reacted positively, there was marked erythema and edematous induration. In sensitized guinea pigs the reaction is characterized by a violent inflammatory response with neutrophilic infiltration and much edema. The reaction is well developed 6 hours after injection, but is most marked on the 3d day, after which it regresses rapidly.<sup>17</sup> Negative cases showed no changes. The opsonocytophagic test was carried out by the technique described by Huddleson.<sup>9</sup> Agglutinative and complement fixation tests were made with the technique described by one of us previously,<sup>16</sup> modified by using purified brucella protein as antigen in the complement fixation tests.

**Material.** Three groups were tested. Group A consisted of 222 adult males from Puerto Rico working in contact with cattle or infected material as milkers or cattle handlers near San Juan. Group B was composed of 1003 children and adults from the general population of San Juan, whose milk supply is infected with *Br. abortus*. Group C was composed of 448 children and adults from the general population of St. Thomas, where abortion disease is not known to exist.

**Results.** Of the 222 adults of Group A 35.5% reacted to one or more of the tests made, 24.7% showed hypersensitiveness, 20.2% showed a positive opsonocytophagic reaction, 5.4% showed positive agglutination and 7.2% showed a positive complement fixation reaction.

Of the 1003 cases of Group B 5% reacted positively to one or more of the tests, 4.2% gave a positive cutaneous reaction, 2.3% showed a positive opsonocytophagic reaction, while 0.29% were positive to agglutination and 0.49% showed a positive reaction to the complement fixation test.

Of the 448 children and adults from the general population of St. Thomas, where endemic abortion is not known to exist, all cases were negative to the skin test, agglutination and complement fixation reactions. One per cent gave positive opsonocytophagic reaction. Two cases suffering of advanced pulmonary tuberculosis showed  $\pm$  reactions to the skin test, but in both instances the reaction was considered negative and the cases were negative to all other tests (see table).

TABLE 1.—CORRELATION OF BRUCELLOSIS TESTS IN A CONTACT GROUP AND GROUPS FROM THE GENERAL POPULATION.

Groups tested.	Contact group (P. R.)	Group from general population of P. R.	Group from general population of St. Thomas.
Number of persons tested . . . . .	222	1003	448
Reactors to one or more tests, % . . . . .	35.5	5.0	2.2
Reactors to skin test, % . . . . .	24.7	4.2	0
Reactors to agglutinative test, % . . . . .	5.4	0.29	0
Reactors to complement fixation test, % . . . . .	7.2	0.49	0
Reactors to opsonocytophagic test, % . . . . .	20.2	2.3	2.2
Clinical evidence, % . . . . .	3.3	0.3	0

Total number of persons tested, 1673

**Discussion.** There is no correlation between cutaneous allergy to brucella infection and other immunological reactions such as agglutination or complement fixation.

As in Evans' report,<sup>5</sup> in our series there were cases positive to the opsonocytophagic test, which gave a negative cutaneous reaction, and cases showing a positive cutaneous reaction which were negative to the opsonocytophagic test. Others were positive to both and negative to agglutination or complement fixation. It is worthy of note that in our series, using the purified protein as an antigen, the number of cases giving a positive reaction to the complement fixation test was larger than that giving a positive agglutination. In experimental work published by one of us,<sup>16</sup> it was demonstrated that agglutinins in rabbits develop earlier and disappear earlier from the blood than alexins.

Using the purified brucella protein for cutaneous tests in this series, none of the cases showed necrosis, although 8% of the positive reactors developed constitutional reaction accompanied by pain or discomfort in the arm, general malaise and slight fever, which usually lasted 24 hours. Severe local and systemic reactions were absent.

There is a direct relation between contact with infected sources or ingestion of infected raw products and skin reaction to the purified brucella protein.

Contact with infected material may cause the development of a state of hypersensitiveness as shown by injection of purified brucella protein, although clinical signs or symptoms of the disease may not have been evidenced.<sup>5,14</sup> Other cases may show laboratory and clinical evidence of infection by brucella organisms, and yet do not show hypersensitiveness;<sup>5,14</sup> still others may have been in contact with sources of infection for many years and show symptoms of previous latent infection and give a negative reaction to the injection of brucella protein. In the case of anergy in the presence of proven brucella infection, clinical and laboratory evidence may precede the development of a positive reaction. This may merely represent a delay in the appearance of allergy and these cases should be tested from time to time to see if hypersensitiveness develops some time during infection.

Desensitization apparently occurs. We observed that usually the older milkers and those that had been working in an infected dairy for many years, were negative to the cutaneous test, although they, undoubtedly, had chances of becoming infected. In some cases they were positive to one of the other reactions, but usually they were negative to all of them.

The possibility of sensitization without infection must be duly considered in evaluating the skin reaction. No doubt there is a necessity for a standard preparation that will react with specificity, stability and constant potency, and it is hoped that the purified brucella protein may fulfill this need.

In our opinion, the cutaneous test to the purified brucella protein, when positive, only occurs in persons that have been previously



sensitized to brucella protein. It should be of great value in epidemiological investigations in determining the persons that have been in contact with infected sources, but until further work is done it should not be considered as proof of present or past infection, since it only shows a state of hypersensitiveness in persons that have been in close contact with infected material.

From the practical standpoint, it seems doubtful if there is as much significance in determining how many have ever been infected with brucella as in finding how many harbor the bacilli at the moment. Whether or not this can be done remains to be proved.

**Conclusions.** 1. A method for the preparation of a purified protein derivative from brucella cells is described. The product obtained is of a fine consistency, light brown in color, of a fairly constant chemical composition, can be measured accurately and constitutes a good antigen.

2. The preparation has been used successfully as an antigen in complement fixation tests and in determining cutaneous hypersensitiveness to brucella in man and laboratory animals.

3. In man there is a direct relation between contact with infected material or ingestion of infected raw products and skin reaction to purified brucella protein.

4. The incidence of positive reactors to the skin test in Puerto Rico, where *Br. abortus* infection is prevalent in cattle, was 24.7% in contact groups and 4.2% in groups from the general population consuming raw milk from infected sources. On the island of St. Thomas, where infection is not known to exist, we were unable to find any reactors in the group examined.

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## EXPERIMENTAL HYPERTENSION IN NEPHRECTOMIZED PARABIOTIC RATS.

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THE study of experimental arterial hypertension which will result from constriction of the renal artery by Goldblatt's method has led to the inference that the likely cause for the elevation of blood pressure is a pressor substance elaborated by the affected kidney.<sup>5</sup> An alternative possibility needs still to be considered: that the presence of a presumably altered kidney may result in the diminished destruction or excretion of pressor substances formed elsewhere than in the kidney.

We have been able to confirm the fact that 2 rats living as Siamese twins, with interchange of their capillary and lymphatic fluids as demonstrated by anatomic<sup>3</sup> and physiologic<sup>11</sup> studies, will survive in the total absence of renal tissue from one of the two parabiotic animals.<sup>10</sup> This type of preparation seemed favorable for an approach to testing the second hypothesis mentioned: if the excretion of pressor substances formed outside the kidney were impaired by the reduction of renal tissue, then one or both parabionts might show hypertension. Such a result, however, might be dependent upon other mechanisms, such as fluid retention with an associated increase in blood volume.

**Method.** Litter mate male rats were joined together by the method of Bunster and Meyer<sup>2</sup> when they were 20 to 30 days old. In some instances one kidney was removed from one or both animals at the time of joining. After 60 to 90 days further nephrectomies were performed until only one kidney remained to function for both animals.

Estimations of systolic blood pressure were made by the method of Griffith,<sup>6a</sup> using soluble Evipal (N-methylcyclohexenylmethyl barbituric acid) intraperitoneally (7 mg. per 100 gm. body weight), to obtain a brief period of light anesthesia. The blood pressure was taken prior to each successive nephrectomy in the adult animals, and usually daily following the third nephrectomy for as long as the animals survived. In our hands this indirect method of estimating blood pressure has shown a tendency

to give lower readings than the more accurate method of Hamilton, Brewer and Brotman.<sup>8</sup>

In another series of parabionts blood volume was determined by the method of Griffith and Campbell,<sup>7</sup> before each nephrectomy in the adult parabionts, and weekly after the third nephrectomy. The animals were anesthetized as for the taking of blood pressure, and injections were made into the femoral or jugular veins. Microchemical determinations of the blood urea nitrogen were made by the Folin method.<sup>4</sup>

The animals were allowed to drink water as desired and likewise to eat an unmeasured quantity of Purina Dog Chow supplemented by a semi-weekly ration of cabbage and celery leaves and carrot roots.

The weight of each parabiont was obtained by carefully placing the anesthetized animals on two adjacent scales. The sum of the individual weights was found to approximate the weight of both animals on a single scale by an error of not more than 5 gm.

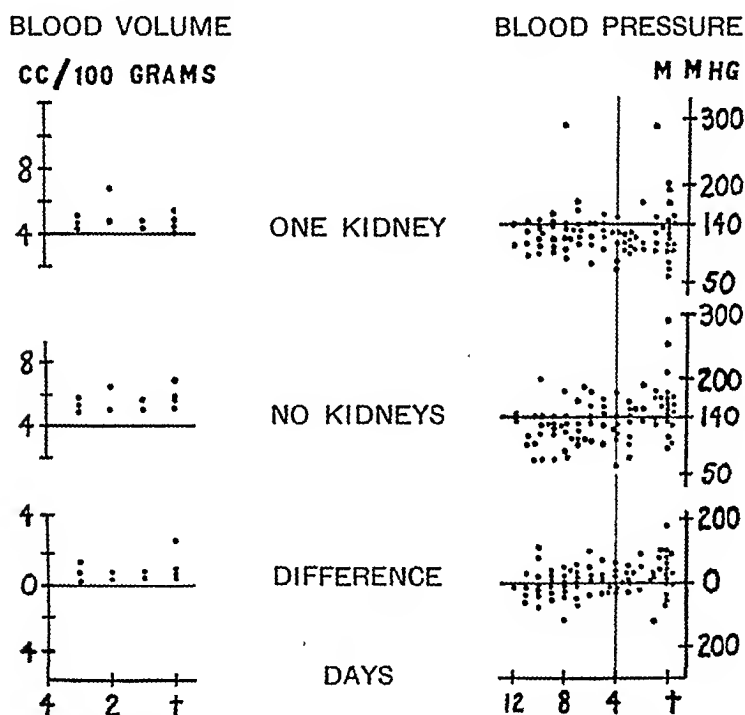


CHART 1.—A comparison between blood volume of 11 pairs of parabiotic rats, and systolic blood pressure of 19 pairs of parabiotic rats, toward the end of their survival period.

In the top section on either side are values for parabiotic twins retaining one kidney (the other member of the pair having no kidneys); the middle section records the same features for totally nephrectomized animals (the other member of the pair having one kidney); while the bottom section shows the arithmetical difference between the values above, *i. e.*, doubly minus singly nephrectomized. The doubly nephrectomized animals invariably show a larger blood volume, and usually exhibit higher blood pressure.

**Results.** Following the removal of the third kidney the twin rats will live for as long as 3 months. However, with repeated anesthetics for the taking of blood pressure and blood samples, the

median survival of 19 pairs of rats was 10 days. In the last week of life the totally nephrectomized animal showed increasing elevation of blood urea nitrogen, while its parabiont retaining one kidney showed only slight azotemia at most.<sup>10</sup> There was usually progressive weight loss following the third nephrectomy. At necropsy the first of the pair to die showed visceral congestion, ascites and hydrothorax being found in 8 instances. The totally nephrectomized animal was usually the first to die.

Prior to the third nephrectomy no marked variations between the blood pressures of the two parabionts were observed. After the third nephrectomy, however, 13 of 19 pairs of rats showed a terminal elevation of systolic blood pressure to 140 mm. Hg or more, in 10 instances the higher pressure being exhibited by the totally nephrectomized animal. Seven of the 8 animals showing serous effusions had terminal hypertension. All blood pressure readings taken during the last 12 days before death are recorded for 19 pairs of animals in Chart 1.

TABLE 1.—BLOOD VOLUME IN SINGLE AND PARABIOTIC RATS. THE MEAN BLOOD VOLUME OF PARABIOTIC PARTNERS WITH BOTH KIDNEYS REMOVED IS SIGNIFICANTLY ELEVATED.

	Single.			Parabiotic.			
	Intact.	One kidney.	24 hours after both kidneys out.	Intact.	One kidney out of each.	Partners.	
						One kidney out.	Both kidneys out.
Number of observations . . . .	4	6	4	47	22	11	11
Mean blood volume cc. per 100 gm. .	4.9 ± .14*	4.19 ± .12	5.0 ± .17	4.95 ± .11	4.86 ± .13	4.7 ± .21	5.71 ± .23
Incidence of blood volume of more than 5.5	0	0	0	9	3	1	7

\* Standard error of the mean.

Blood volume determinations were made upon a second series of both single and parabiotic rats after one or both kidneys had been removed. The results for each type of preparation are seen in Table 1. Because of the necessity for exposing and puncturing the femoral veins when repeated estimations of blood volume were made, no blood pressure readings were attempted on this series of animals. Comparing the two series, in the last 4 days of life the totally nephrectomized animal showed a significantly preponderant incidence

of hypertension, and in every parabiotic pair studied there was a higher blood volume. This, together with the degree to which the totally nephrectomized rats' blood volume and blood pressure are increased, is shown in Chart 1.

**Discussion.** Parabiosis, as produced in rats, has afforded the opportunity to observe changes in blood pressure and blood volume following nephrectomy over a longer period of time than the single animal would survive. The frequent occurrence of hypertension in the totally nephrectomized parabiotic rat is in contrast with the usual behavior of individual dogs as shown by Harrison, Mason, Resnik and Rainey.<sup>9</sup> To the best of our knowledge, ours are the first experiments in which hypertension has been observed to occur frequently in totally nephrectomized animals. Beckmann, Basz, Dürr, and Drosihn<sup>1</sup> have demonstrated an increase in the blood volume of dogs 48 hours after nephrectomy. Miller and Williams<sup>12</sup> observed marked elevations of blood pressure upon giving large quantities of fluid to patients with hypertension and with nephritis. Griffith,<sup>6</sup> using a somewhat similar technique in rats, has shown the rise in blood pressure to be accompanied by an increased blood volume.

In the light of the foregoing references, hypervolemia seems to be at least an important factor in the production of high blood pressure late in the survival period of the totally nephrectomized parabiotic rats. If the retention of pressor substances is a factor, their effects could be only contributory.

**Summary.** Totally nephrectomized rats will survive in parabiosis for 2 to 90 days following the second nephrectomy. They will show progressive weight loss and azotemia in the last week of life. Terminally hypervolemia and hypertension will usually appear. The probable mechanism of this type of experimental hypertension is discussed.

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**HYPERTENSION, BODY BUILD AND OBESITY.\***

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THE relationship of obesity to hypertension is still a moot question and its exact significance awaits further clarification. There is no question but that there is a positive statistical correlation between obesity and hypertension. In any large group there will be more systolic and diastolic hypertension in the obese members and fewer low pressures than in the non-obese.<sup>4-8,10,13,20,21</sup> Further, in any hypertensive group there will be almost three times more overweights than underweights. Clinically, too, the relationship is demonstrated by the lowering of the blood pressure of obese patients when weight reduction is effected.<sup>1,14,15</sup> In spite of this it has not been implied that obesity causes hypertension for there are some underweights who are hypertensive and some overweights who have low pressures. The most that can be concluded from the statistical and clinical relationships is that there may be something about obesity that aggravates an inherited predisposition to hypertension. If it is not the obesity itself, then the altered metabolism associated with obesity may be a contributing factor that aggravates a latent hypertension. Even such inferences are not final. Several extraneous and disturbing factors enter into the picture. One of the most important is the rôle of body build. Body build of itself is definitely related to weight and blood pressure.<sup>2,9,11,12,16,22</sup> Before we can fully assess the obesity factor in hypertension, it must be separated from its dependence upon body build which also asserts an unfavorable influence on blood pressure. It is the purpose of this paper to consider the effect of both of these forces by separating the weight from the build factor and determining the relative influence of each in their correlations to hypertension.

In two previous papers hypertension was shown to be positively correlated to both obesity<sup>19</sup> and body build.<sup>18b,c</sup> In this study the records of the periodic physical examinations of 3436 men and 2184 women were analyzed. A complete description of the source material, the method of examination and the composition of the group has been published.<sup>18a</sup>

\* A portion of this material was exhibited at the St. Louis Sessions of the American Medical Association, 1939, and the Inter-State Post Graduate Assembly, Chicago, 1939. Assistance in the preparation of these materials, tables, and charts was furnished by the personnel of the Work Projects Administration, Official Project No. 465-54-3-37 (3).

We showed previously that weight alone was not an accurate measure of obesity, so we used the ponderal index-weight divided by height. In this paper we introduce chest circumference as a further corrective factor in defining obesity by using a modified ponderal index,  $\frac{\text{weight} \times 100}{\text{height} \times \text{chest circumference}}$ . \* This index adjusts for both height and width, allowing the taller or broader person to carry more weight and the shorter or more slender person to carry less weight and be classified as normal. Body build is measured by the simple ratio of chest circumference to height.† It will be noted that weight is not used to arrive at a build index.

First, in this study, we divided our sample into four build groups, at one extreme the linear or slender and at the other extreme the lateral or broad. The portion between the extremes was broken into two intermediate groups. Each of these four build groups, in turn, was divided into light, medium, and heavyweight subgroups as shown in Table 1.

TABLE 1.—THE INCIDENCE OF WEIGHT CLASSES IN BODY BUILD GROUPS IN 3436 MEN AND 2184 WOMEN.

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Lightweight	267 (49%)	261 (40%)	311 (23%)	165 (21%)	117 (11%)	36 (8%)	8 (2%)	9 (3%)
Mediumweight	262 (48%)	355 (55%)	965 (71%)	498 (63%)	851 (75%)	252 (54%)	252 (61%)	83 (30%)
Heavyweight	15 (3%)	35 (5%)	75 (6%)	127 (16%)	163 (14%)	176 (38%)	150 (37%)	187 (67%)
Total	544	651	1351	790	1131	464	410	279

A study of the weight distribution within each build group showed the tendency for the broad or lateral build group to have a far greater incidence of obesity than did the linear or slender build group. As is apparent from Table 1, as the group becomes more lateral or broad the incidence of obesity increases markedly and there is a proportionate decrease in the incidence of lightweight. For example, consider the striking fact that 37% of lateral or broad-chested men are obese, while 3% linear or slender are obese. On the other hand, only 2% of lateral men are lightweight while 49% of linear men are lightweight. This same strong affinity of the

\* In the present paper the weight classes are defined as follows:

Lightweight = Modified Ponderal Index under 6.00

Mediumweight = Modified Ponderal Index 6.00 to 6.99

Heavyweight = Modified Ponderal Index 7.00 and over

A full discussion of the weight breakdowns is found in Reference 19.

† In the present paper the body build types are defined as follows:

Linear build = chest:height ratio less than .50

Linear intermediate build = chest:height ratio between .50-.54

Lateral intermediate build = chest:height ratio between .55-.59

Lateral build = chest:height ratio .60 and over

lateral build for obesity is present to an even more marked extent among women.

It is therefore very apparent that obesity is an attribute of build. The chances of a lateral or broad type individual being underweight are slight and the chances of the slender or linear build person being overweight are slight. Obesity is therefore dependent to a great extent upon the build of the individual and denotes more particularly the broad-chested person.

**Mean Systolic and Diastolic Pressures in Specific Weight-build Groups.** When the effect of obesity on blood pressure in a total group in which there is a conglomerate of mixed builds is studied, there is a very significant correlation between body weight and blood pressure. However, if obesity is to be considered an etiologic factor in hypertension or even a contributing factor, then an increase in blood pressure must be noted as the weight increases in every specific build group. To examine this contention let us first study the changes in mean systolic pressure as the weight varies in each build group. In Table 2 it can be seen that with a procession from light to heavyweight there is not always a proportionate increase in systolic pressure. There is a slight increase in systolic pressure with weight in the linear or slender builds for both men and women but in the lateral intermediate men and the lateral build women this does not occur. As a matter of fact there is actually a reversal of the expected trend, while in the remaining builds the difference between light and heavyweight is too small to be significant.

TABLE 2.—MEAN SYSTOLIC PRESSURE IN SPECIFIC WEIGHT-BUILD GROUPS IN 3436 MEN AND 2184 WOMEN.

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Lightweight . . . . .	116	109	120	113	134	121	136*	141*
Mediumweight . . . . .	118	113	120	118	129	127	133	143
Heavyweight . . . . .	120*	112	124	120	125	125	134	135

\* Less than 30 persons.

In diastolic pressure there is a better correlation of weight to blood pressure in the respective build groups (Table 3). The obese men in every build group showed a slightly higher mean diastolic pressure than did the lighter weight men, although the more slender women showed no difference and the lateral women a probable reversal of trend.

On the other hand, a very definite and consistent relationship is observed between body build and mean systolic and diastolic pressure in every weight group. Progressing from linear to lateral



build the men show a steady increase in systolic and diastolic pressure in every weight group, and the women do likewise to an even more marked degree. Equally significant is the fact that the increase in pressure is consistently greater as the group becomes broader chested than it is when the group becomes heavier. For example, the greatest increase in pressure caused by an increase from light to heavyweight among women was 7 mm., while the greatest increase from slender to broad build was 30 mm. The mean increase in systolic pressure due to weight for men and women was 1 mm. and that due to build was 27 mm.; the mean diastolic increase due to weight was 4 mm., that due to build was 11 mm. This fact illustrates immediately the relative importance of obesity and build. Another interesting observation, though not bearing on this study, is that the linear types of women have lower pressures than the linear types of men while in the lateral types they tend to be almost equal.

TABLE 3.—MEAN DIASTOLIC PRESSURE IN SPECIFIC WEIGHT-BUILD GROUPS IN 3436 MEN AND 2184 WOMEN.

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Lightweight . . . . .	70	67	73	68	77	75	80*	79*
Mediumweight . . . . .	71	69	75	72	79	76	81	81
Heavyweight . . . . .	77*	68	78	73	80	76	87	81

\* Less than 30 persons.

**The Incidence of High Pressures in Specific Weight-build Groups.** A more illustrative picture of the effect of weight and build upon blood pressure is to be found in the comparison of the incidence of hypertension within each specific weight-build group. It would be expected that the incidence of systolic hypertension would increase with an increase in weight in all build groups. Chart 1 shows that this is not always the case. The incidence of hypertension rises as obesity increases in the linear or slender build groups but fails to follow this trend in the lateral groups. There is an actual reversal of the trend in some of the broad chested groups revealing less hypertension in the obese than in the underweight.

The distribution of diastolic hypertensives showed a more consistent correlation to obesity among men (Table 4). In every build there is a steady increase in the incidence of diastolic hypertension as the group becomes heavier, but the women do not show this correlation. Only in the linear intermediate group is the expected trend observed. All other groups of women show a minimal expected trend or no difference at all.

On the other hand, the effect of build upon systolic and diastolic hypertension shows a consistent and unmistakable tendency. Both

men and women become more susceptible to high systolic and diastolic pressure as they fit into the broader build groups. There is more than a 100% increase in the incidence of hypertension as the group progresses from the extreme linear to the extreme lateral build. The women show 300% and 400% increases in the incidence of hypertension. The same trend is present in diastolic hypertension.

TABLE 4.—THE INCIDENCE OF HIGH DIASTOLIC PRESSURE (OVER 80 MM.) IN SPECIFIC WEIGHT-BUILD GROUPS IN 3436 MEN AND 2184 WOMEN.

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Lightweight . . . . .	15%	10%	23%	10%	33%	31%	38%*	44%*
Mediumweight . . . . .	22%	13%	30%	22%	41%	38%	52%	61%
Heavyweight . . . . .	33%*	11%	39%	25%	45%	35%	57%	51%

\* Less than 30 persons.

Body build exerts a constant and almost proportionate effect on both systolic and diastolic hypertension. The broader persons are unfavorably affected. On the other hand, obesity was shown to be correlated to diastolic hypertension among the men and less so to systolic pressure. Among the women obesity shows an inconstant effect on hypertension; in some groups there is a positive correlation and in others none at all or an actual reversal of the expected trend.

**The Incidence of Low Pressures in Specific Weight-build Groups.** In those groups where the incidence of hypertension increases it is to be expected that the incidence of low pressure will decrease. This is true in most instances. The incidence of low systolic pressure is smaller in the heavyweight groups of the more linear or slender men and women. The linear builds therefore do show a low pressure—lightweight correlation. In the more lateral builds the obese men actually had slightly more low systolic pressure than the lightweights, while the women showed a slight tendency towards a decreased incidence of low pressure in the heavyweight group. The lateral builds, therefore, do not show a low pressure—lightweight relation (see Charts 1 and 2).

The incidence of low diastolic pressures in the obese men is always slightly lower than in the lightweight men of any build group; the expected trend holds true. However, in diastolic as in systolic pressure, lightweight and low pressure are correlated only in the linear intermediate women. All other types of women failed to show the expected trend (Table 5).

On the other hand, the build factor exerts a constant effect upon the incidence of low blood pressure. In every weight group for both men and women—with one exception in heavyweight men—the

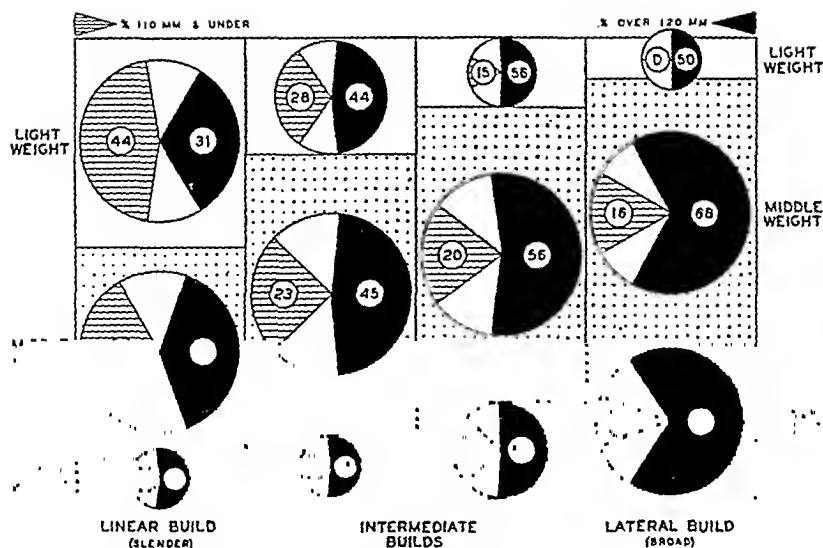


CHART 1.—The relative influence of obesity and body build on high and low systolic pressures in 3436 men. Of the four body build groups, the extreme linear is on the left and the extreme lateral is on the right. Each body build group, in turn, is divided into lightweight (blank space), mediumweight (dotted space), and heavy-weight (cross-hatched space). Within each specific weight-build group the shaded section of the circle denotes the percentage of low systolic pressure, and the black section denotes the percentage of high systolic pressure. Moving from linear on the left to lateral on the right, the black sections of hypertension show a greater increase than they do when moving from lightweight to heavyweight. Lightweight are found predominantly in the linear build, while heavyweights are found predominantly in the lateral build.

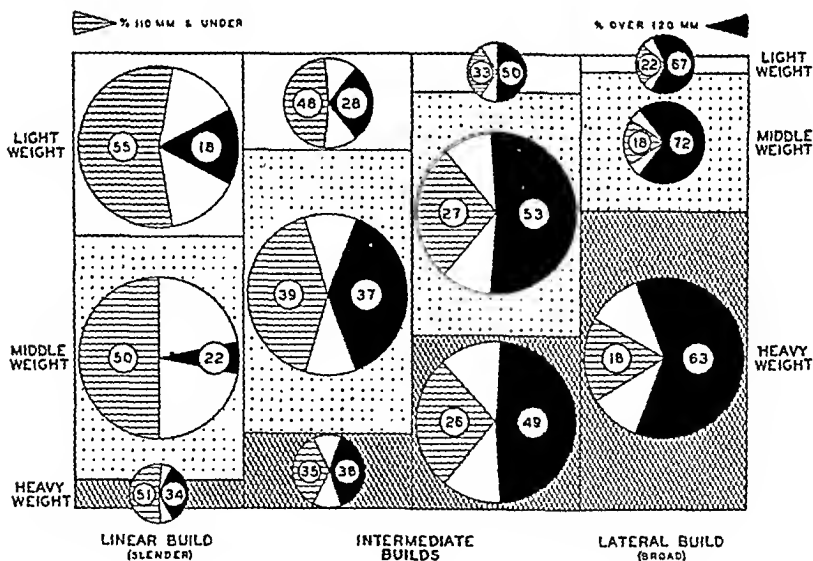


CHART 2.—The relative influence of obesity and body build on high and low systolic pressures in 2184 women. Construction is the same as in Chart 1. Moving from linear on the left to lateral on the right, the black sections of hypertension show a greater increase than they do when moving from lightweight to heavyweight. Lightweight are found predominantly in the linear build, while heavyweights are found predominantly in the lateral build. (Charts prepared by W. P. A. project 465-54-3-3753.)

lateral person shows a markedly lower incidence of low systolic blood pressure than does the linear or slender person. In one possible exception, the heavyweight men, there is a similar tendency but not to as marked a degree. The effect of build upon the incidence of low diastolic pressure is similar to that of low systolic pressure with the exception, again, that medium and heavyweight men show the expected tendency to a less marked degree.

TABLE 5.—THE INCIDENCE OF LOW DIASTOLIC PRESSURE (UNDER 65 MM.) IN WEIGHT-BUILD GROUPS IN 3436 MEN AND 2184 WOMEN.

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Lightweight . . . . .	37%	48%	22%	43%	19%	22%	0*	33%*
Mediumweight . . . . .	21%	45%	19%	35%	14%	21%	15%	15%
Heavyweight . . . . .	27%*	40%	9%	33%	9%	21%	10%	17%

\* Less than 30 persons.

TABLE 6.—CORRELATION DATA, THE RELATIONSHIPS OF CHEST/HEIGHT, PONDERAL INDEX, AND BLOOD PRESSURE.

Chest/height to systolic pressure . . . . .	{ Men $r = .184 \pm .022$ Women $r = .299 \pm .022$
Chest/height to diastolic pressure . . . . .	{ Men $r = .249 \pm .022$ Women $r = .279 \pm .022$
Modified ponderal index to systolic pressure . . . . .	{ Men $r = .160 \pm .023$ Women $r = .187 \pm .023$
Modified ponderal index to diastolic pressure . . . . .	{ Men $r = .221 \pm .022$ Women $r = .228 \pm .022$
Modified ponderal to chest/height . . . . .	{ Men $r = .467 \pm .018$ Women $r = .539 \pm .017$
Modified ponderal index to systolic pressure (Linear persons only, $\frac{\text{chest}}{\text{height}}$ ratio under 0.55)	{ Men $r = .073 \pm .023$ Women $r = .128 \pm .026$
Modified ponderal index to systolic pressure (Lateral persons only, $\frac{\text{chest}}{\text{height}}$ ratio 0.55 and over)	{ Men $r = .016 \pm .025$ Women $r = .033 \pm .037$
Modified ponderal index to diastolic pressure (Linear persons only, $\frac{\text{chest}}{\text{height}}$ ratio under 0.55)	{ Men $r = .149 \pm .022$ Women $r = .137 \pm .026$
Modified ponderal index to diastolic pressure (Lateral persons only, $\frac{\text{chest}}{\text{height}}$ ratio 0.55 and over)	{ Men $r = .111 \pm .025$ Women $r = .084 \pm .036$

Body build, therefore, exerts a marked constant effect upon the incidence of low systolic and diastolic blood pressure. The lateral person has a lesser chance of having a low pressure than does the linear person. Obese men had less low pressure only in the linear type builds and even where the effect is most marked it is minimal compared to the effect of body build.

The same statistical treatment was made in different age groups with essentially the same results as given for the total group. A study of all age groups should, if anything, yield results more favorable to the obesity-hypertension correlation since the incidence of

both increases with age. The obesity-hypertension correlation is less strong in the age groups 40-54 and 55 and over than in the 25-39 group.

Further treatment of the data with more advanced statistical techniques bears out the conclusions of the previous discussion (Table 6).

To summarize briefly the many statistical tables which show the various inter-correlations between hypertension, obesity and body build Table 7 was constructed. It is apparent from a glance that body build shows an almost complete triple plus or marked correlation with blood pressure in all weight groups. On the other hand, obesity never shows a triple plus relation to blood pressure and only rarely a double plus. Frequently there is no correlation or an actual reversal of the expected trend.

TABLE 7.—A. THE RELATIONSHIP OF OBESITY TO HYPERTENSION.

(The relative strength of expected trend with progression from light to heavyweight in specific build groups. This table shows the inconstant effect of obesity on blood pressure.)

	Linear build (slender).		Linear intermediate.		Lateral intermediate.		Lateral build (broad).	
	Men.	Women.	Men.	Women.	Men.	Women.	Men.	Women.
Mean systolic pressure . . . . .	+	+	+	++	--	+	0	--
% low systolic pressure (under 110 mm.) .	+	+	+	++	-	+	+	0
% high systolic pressure (120 mm. and over)	++	++	+	+	-	0	+	-
Mean diastolic pressure . . . . .	+	0	+	+	+	0	++	0
% low diastolic pressure (under 65 mm.) .	+	+	++	+	+	0	+	-
% high diastolic pressure (80 and over) .	++	0	++	++	++	+	+	-

B. THE RELATIONSHIP OF BODY BUILD TO HYPERTENSION.

(The relative strength of expected trend with progression from linear to lateral build in specific weight groups. This table shows the marked constant effect of body build on blood pressure.)

	Lightweight.		Mediumweight.		Heavyweight.	
	Men.	Women.	Men.	Women.	Men.	Women.
Mean systolic pressure . . . . .	+++	+++	+++	+++	+++	+++
% low systolic pressure (under 110 mm.) .	+++	+++	+++	+++	+	+++
% high systolic pressure (120 mm. and over) .	+++	+++	+++	+++	+++	+++
Mean diastolic pressure . . . . .	+++	+++	+++	+++	+++	+++
% low diastolic pressure (under 65 mm.) .	+++	+++	+	+++	+	+++
% high diastolic pressure (80 mm. and over) .	+++	+++	+++	+++	+++	+++

+++ Marked correlation, ++ good correlation, + slight correlation, 0 no correlation, - slight reverse correlation, -- marked reverse correlation.

**Discussion.** In a previous study we showed that obesity was related to hypertension. In a later publication we reported the correlation of body build to blood pressure as of even greater importance than the obesity-blood pressure correlation. Further study showed that obesity was itself related to body build which immediately presented the question as to which of the two factors was influencing blood pressure and if both, what was the extent of each.

The fact that obesity and body build are themselves highly inter-correlated is of outstanding importance in any attempt to evaluate the relative effects of obesity and body build upon hypertension. Obesity is an attribute of the lateral or broad build. Conversely, underweight is an attribute of the linear or slender build. It should be emphasized that the person born into the lateral build type, the individual with a broad chest, can be regarded as carrying a genotypic affinity for obesity, although this obesity may not become manifest until the last half of the life span. According to this concept the germ plasm which transmits the build type also transmits the characteristic weight tendency for that build type. Obesity, therefore, depends upon the lateral build, and is bound up with the sthenic habitus. Because of this high correlation it was necessary to separate the two factors; the effect of weight upon blood pressure must be studied within a homogenous build group and the effect of build upon blood pressure must be studied within a homogenous weight group.

Body build is shown to exert a striking effect on blood pressure. When the weight factor is carefully held constant it becomes evident that no matter what the weight group, be it light, medium, or heavy, both mean systolic and mean diastolic pressures significantly increase as the group broadens out into the lateral or broad build. The broad-chested individuals in the lateral build group have a higher average blood pressure, a greater incidence of hypertension and a lesser incidence of low pressures than do the linear or slender build or for that matter any other build in any weight group. This emphasizes the strong influence of build upon blood pressure, for it is evident that the greatest incidence of hypertension and the highest mean pressure is found in the lateral type individual regardless of his weight. Thus, it follows that hypertension is part of the broad-chested person's endowment and although obesity, too, is a part of the same pattern it is not the influencing factor in hypertension. It is of interest to note that blood pressure is not the only factor influenced by build. Individuals of the linear or slender build are predisposed to such diseases as gastro-duodenal ulcer and thyrotoxicosis (with minor exceptions),<sup>17</sup> whereas individuals of the lateral build—relatively free from linear type diseases—are predisposed to cardiovascular disorders and to other degenerative processes such as are found in nephritis, diabetes, and cirrhosis of the liver. This association does not imply that it is the morphologic

factor *per se* which produces the selectivity of disease. Rather the build is the gross morphologic expression of a deep seated genotypic change of the neuro-endocrine system and the biochemical reactions of the entire body.<sup>3</sup>

Obesity, on the other hand, does not show this consistent relationship to hypertension. In some build groups there is no correlation to blood pressure as the weight is increased; in some build groups there is a reversal of the expected trend and in those groups where the correlation is present it is much smaller than is shown by that of the body build. The obese persons in the *linear* group have a lower systolic and diastolic pressure than the underweight persons in the *lateral* group. Obesity shows the greatest correlation to hypertension in the linear or slender groups. However, it is a singular fact, that obesity shows no correlation to hypertension in the broad-chested individual (actually reversing the expected trend in some instances). The broad-chested individual is hypertensive in most instances regardless of his weight.

We then recognize the influence of obesity on hypertension in only the linear groups; even here the strange fact emerges that its rôle is more clear in diastolic than in systolic pressure. Why is there a better relationship in the more stable diastolic pressure and a lesser one in the more sensitive systolic pressure where we usually find changes first? We cannot give an adequate explanation for this discrepancy.

From this study it would seem more safe to look upon obesity as an additional degenerative process superimposed upon a more basic underlying metabolic change—hypertension. Obesity, of itself, cannot initiate hypertension nor does it bear any etiologic relationship, although it may aggravate an existing or latent hypertensive state. Since it affects unfavorably the body economy, obesity will similarly affect any disease. Reduction of weight has a favorable effect upon the whole body metabolism and should therefore improve any diseased state. Hypertension is no exception to this rule, nor is it the only isolated example.

**Conclusions.** 1. The rôle of obesity in hypertension is here evaluated by separating obesity from the body build factor with which it is intimately bound.

2. Obesity is found to be intimately linked to the lateral or broad build type; it occurs infrequently in linear or slender build men and women. Of broad-chested men 37% are heavyweight, whereas only 3% of slender men are heavyweight.

3. Body build is shown to be closely correlated with hypertension. In any weight group the broad-chested individuals show the highest mean systolic and diastolic pressures, the greatest incidence of hypertension, and the lowest incidence of low blood pressures.

4. When the build groups are held constant obesity shows an uncertain correlation with hypertension. In those instances where

a positive correlation to blood pressure is demonstrated, it is strikingly less significant than the build correlations in nearly every instance.

5. Obesity shows its greatest correlation to blood pressure in the linear or slender build groups. In the lateral or broad groups no correlation is noted; sometimes there is a reversal of the expected trend.

6. Therefore, body build is the true genotypic factor which, regardless of his weight, determines in a great measure the predisposition of any individual to hypertension.

7. The rôle of obesity in hypertension is found to be small. The current widely accepted rôle of obesity must be reevaluated.

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#### THE EFFECT OF LARGE DOSES OF INSULIN ON GLUCOSE TOLERANCE.\*

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AN opportunity to study the effects of large doses of insulin on individuals with normal carbohydrate metabolism was provided by the so-called insulin shock treatment for schizophrenia. In this treatment, doses of insulin ranging from 10 to 200 or more units are given daily for as long as 2 months to individuals in order to produce a state of insulin shock following each injection. The

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question arises whether such large doses do not affect the carbohydrate metabolism of the individuals to whom they are given. Various workers,<sup>1,3,9,11,12</sup> have shown that the administration of much smaller amounts of insulin to individuals with normal carbohydrate metabolism in an effort to stimulate appetite results in a decreased carbohydrate tolerance. Looney and Cameron,<sup>7</sup> Harris, Blalock and Horwitz,<sup>6</sup> showed the development of decreased tolerance during insulin shock treatment. Freed *et al.*<sup>5</sup> found both a decreased and increased tolerance.

This paper presents further data on this subject. Glucose tolerance tests were performed on 27 patients undergoing insulin shock treatment at the Pennsylvania Hospital for Mental Diseases. None of the patients had diabetes or any physical abnormalities which could be felt to affect carbohydrate metabolism with the exception of one with a history of alcoholism whose liver was enlarged.

**Method.** The patients were given insulin at 7.30 A.M. each day, Sundays excepted; at 10 A.M. to 12.00 noon, depending on the patient's condition, the insulin reaction was terminated by oral or intravenous glucose followed by breakfast. Starting with an initial dose of 10 to 20 units, this was increased daily by 10 to 20 units until "coma" was regularly produced. This usually occurred with doses ranging from 100 to 200 units. This dose was then given daily for 5 to 10 "comas" at which time most patients had reached a state of hypersensitivity to insulin; the dose could be reduced 50 to 100 units less than the original coma dose with apparently the same clinical reaction. The patients were then carried on this reduced dose until the desired number of treatments had been given.<sup>10</sup> The total dosage during the course of treatment ranged from 1040 to 7630 units. Each patient was in a state of hypoglycemia for 3 to 5 hours daily, with blood glucose ranging between 10 to 40 mg. per 100 cc. as measured by the Folin-Wu method on venous blood.

The insulin reaction was terminated daily by injecting 50 or 100 cc. of 25% glucose intravenously. Also each patient received orally 2 gm. of glucose for each unit of insulin injected.

Before treatment patients were on a house diet of C 420, P 100, F 130 (3250 calories). During treatment patients received similar diet augmented by extra feedings, and glucose used to terminate treatment reaching a total daily intake of 5130 calories.

Patients almost uniformly gained weight during treatment, the average being 10 pounds, while gains of 20 to 34 pounds occurred in the group.

Weekly tests revealed glycosuria in only two instances in all patients at any time, before, during or after the course of treatments.

The glucose tolerance test used was that in which measurement of glucose in venous blood is made with the Folin-Wu method before and at intervals of  $\frac{1}{2}$ , 1, 2 and 3 hours after the injection of 1.75 gm. of glucose per kilo of body weight. Treatment was omitted the day of the tolerance test.

**Results.** Table 1 presents the data on 7 of the 27 cases studied. The entire data of all 27 cases studied, including those presented in Table 1, can be summarized as follows: 1. All curves, with the possible exception of curve 2, are within normal limits in that they return to the base line within 3 hours.

2. The chief finding of note is the development of high curves

during the course of treatment. Maximum rises as high as 230 mg. per 100 cc. venous blood are noted. This maximum rise usually occurs  $\frac{1}{2}$  to 1 hour after injection of glucose.

3. Of the 7 cases in which a control was obtained (Table 1) all show a rise in curves developing during administration of insulin. No case failed to show this rise in curves.

TABLE 1.—DATA ON 7 CASES.

Case.	Time of tolerance test.	Blood sugar, grams %.					Total No. of treatment days.	Total insulin units.	Weight gain during treatment (lbs.).
		Fast-ing.	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	3 hrs.			
1	Control	.086	.110	.115	.074	.090	55	2985	1
	33 days of insulin	.098	...	.152	.175	.115			
	1 day after insulin R	.099	.120	...	.071	.069			
	69 days after insulin R	.099	.150	.162	.130	.087			
2	Control	.075	.130	.090	.100	.115	25	1040	12
	20 days of insulin	.102	.196	.188	.123	.108			
	1 day after insulin R	.087	.155	.101	.099	.077			
	60 days after insulin R	.090	.125	.070	.074	.067			
3	Control	.090	.130	.126	.090	.061	46	5175	8
	22 days of insulin	.074	.187	.197	.205	.101			
	35 days	.071	.210	.185	.140	.079			
	1 day after insulin R	.088	.179	.207	.094	.055			
	15 days after insulin R	.094	.185	.164	.091	.045			
	36 days after insulin R	.075	.155	.178	.105	.055			
4	Control	.090	.127	.104	.085	.097	48	4085	20
	23 days of insulin	.093	.145	.155	.116	.100			
	43 days	.094	.180	.180	.085	.111			
	1 day after insulin R	.086	.168	.153	.095	.059			
	14 days after insulin R	.084	.180	.162	.086	.074			
	70 days after insulin R	.091	.142	.105	.104	.060			
5	Control	.085	.148	.114	.101	.111	49	6985	20
	24 days of insulin	.085	.171	.166	.086	.066			
	44 days of insulin	.090	...	.144	.101	.079			
	1 day after insulin R	.069	.124	.147	.084	.091			
	14 days after insulin R	.092	.160	.161	.105	.080			
6	Control	.087	.116	.130	.104	.077	43	4240	
	26 days of insulin	.115	.168	.117	.137	.110			
	2 days after insulin R	.091	.178	.155	.082	.077			
7	Control	.070	.106	.055	.092	.066	40	4395	18
	13 days of insulin	.079	.116	.129	.090	.061			
	29 days of insulin	.091	.155	.085	.103	.060			
	4 days after insulin R	.076	.123	.140	.084	.064			

4. Of the 11 cases in which it was possible to obtain determinations, all but 2 show a fall in curves in the period following cessation of insulin administration. This fall does not begin in the 2 weeks immediately following cessation of insulin administration

(Cases 3, 4, 5), but is apparent thereafter and has dropped to pre-insulin levels by 2 to 3 months in the majority of cases.

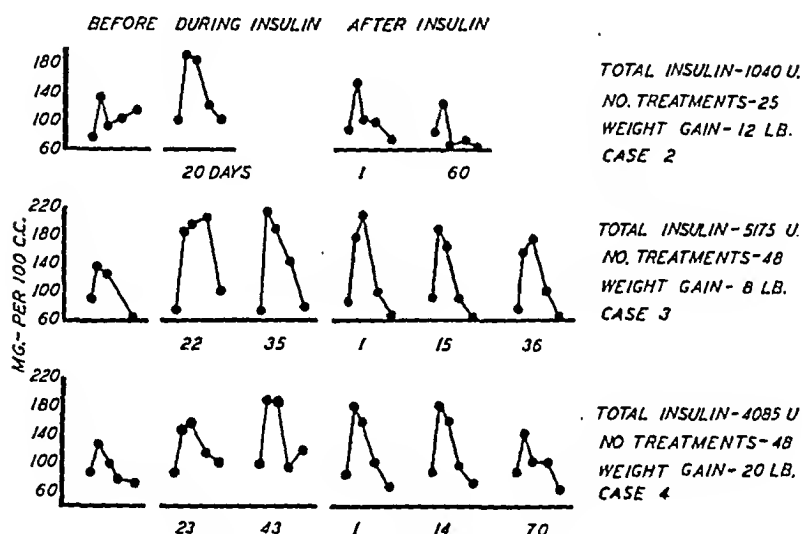


CHART 1.—Three cases illustrating changes in glucose tolerance accompanying a course of insulin.

5. No curves definitely characteristic of increased carbohydrate tolerance are observed.

6. No correlation between the height to which the curves rise and the total dosage of insulin or weight gain during treatment is

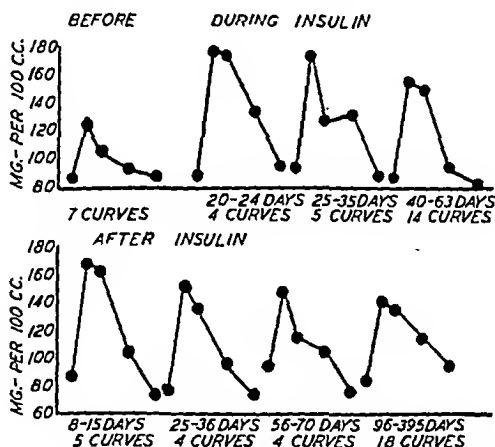


CHART 2.—A composite chart of all glucose tolerance curves taken in this study before, during and after insulin.

apparent. Similarly the degree of sensitivity to insulin developed, the number of comas attained seem to bear no relationship.

Chart 1 presents 3 cases (Cases 2, 3, 4) illustrating the rise in the curves during insulin treatment and the gradual fall during the period following treatment.

Chart 2 is a compendium of all the curves taken in the study.

**Discussion.** The finding of high curves indicating decreased glucose tolerance following large daily doses of insulin is in agreement with the findings of Looney and Cameron<sup>7</sup> and Harris, Blalock and Horwitz.<sup>6</sup> Because of the many factors which influence a glucose tolerance test it is not possible, in the absence of direct experimental evidence, to throw any light on the underlying mechanism behind our results. One possible explanation is that the normal secretion of insulin by the pancreas is inhibited by the large amounts of insulin administered to these patients so that the secretion of insulin by the body is temporarily reduced, thereby giving a high glucose tolerance curve. After the cessation of insulin administration the pancreas resumes its normal insulin secretion and the glucose tolerance curve falls to normal levels. It is recognized this explanation is hypothetical; however, in support of it, is the fact<sup>2</sup> that fasting and low carbohydrate diets produce a rise in the glucose tolerance curve. Conversely high carbohydrate diets result in an augmentation of the utilization of glucose which suggests that the ability of the pancreas to secrete insulin varies with the demand made upon it. McJunkin and Roberts<sup>8</sup> have shown that injections of insulin inhibit mitotic activity of the pancreatic islet cells in young rats.

Cori and Cori<sup>4</sup> have shown that insulin increases the rate of absorption of glucose from the intestinal tract of rats. This offers another explanation of our findings in that an increased rate of absorption of glucose from the intestinal tract theoretically may cause an elevated tolerance curve.

**Summary.** Insulin given over periods as long as 2 months in daily doses large enough to produce coma in patients with normal carbohydrate metabolism results in elevation of glucose tolerance curve. This disappears 2 to 3 months after cessation of insulin administration.

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## THE EFFECT OF ADDED CARBOHYDRATE UPON STABILIZED INSULIN-TREATED DIABETICS.

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PREVIOUSLY to the introduction of insulin it was generally maintained that the treatment of diabetes should be inaugurated by a régime of undernutrition with low carbohydrate intake. Today this plan is still utilized in certain cases. When the urine becomes sugar-free the carbohydrate is slowly increased by from 10 to 25 gm. every 3 to 10 days or even daily. The effect of the diet is judged according to the presence or absence of urinary sugar, and if sugar reappears in the urine, showing lack of carbohydrate utilization, the carbohydrate is either further reduced or the administration of insulin is begun. Adjustments of diet and insulin are subsequently made in order to maintain the carbohydrate intake at about 100 gm. daily. Other writers approve of a much higher ration of carbohydrate with proportionate increase in insulin dosage, the aim being to control the glycosuria by larger doses of insulin instead of by a reduction in dietary carbohydrate.

The substitution of proinsulin for regular insulin has required certain modifications. Patients on proinsulin who have become sugar-free are more apt to have insulin reactions, and to avoid this it has become usual to prescribe excess carbohydrate to act as a buffer against these reactions, but which in turn is apt to cause a varying degree of glycosuria. Some authors state that with proinsulin considerable glycosuria should be permitted, in fact they consider its presence desirable as a protection against reactions, though there is some difference of opinion as to the degree of glycosuria permissible.

We have briefly reviewed the more recent practice in the treatment of diabetes in order to emphasize the fact that when an adequate amount of carbohydrate is prescribed, in all except very mild cases, either larger doses of regular insulin are needed, or, with proinsulin hyperglycemia and glycosuria are usually present at intervals.

The insulin-shock treatment of psychopathic cases has demonstrated that repeated large doses of insulin may have deleterious effects upon the central nervous system, and, on the other hand, the marked hyperglycemia and glycosuria in cases treated with proinsulin (because of the required excess of carbohydrate in the diet), may be harmful in the long run. The ultimate effect upon the

diabetes of proinsulin treatment with its attendant hyperglycemia and glycosuria cannot as yet be definitely stated.

For these reasons it seemed desirable to examine into the possibility that diabetics might be enabled to metabolize an amount of carbohydrate in excess of that allotted according to the usual criteria.

In glucose tolerance tests the blood sugar curve is usually reported, but often there is no report as to the amount of sugar excreted during the test-period and no discussion could be found in the literature as to the late effect, for two or more succeeding days, upon the carbohydrate balance.

The purpose of this investigation was to determine whether certain diabetics could metabolize added carbohydrate without increasing their insulin dosage, if the carbohydrate were given according to a certain schedule.

**Method.** We have studied 9 diabetics. The first 2 (Table 1) were under daily observation for several weeks. The remaining 7 had the test applied only once and will be discussed as a separate group. The first 2, males, had a moderately severe diabetes and had required during weeks or months preceding the test fairly constant amounts of insulin upon a diet up to the limit of their carbohydrate tolerance.

During the day prior to the test they received their usual diet and on the test day, fasting in the morning, 100 gm. of carbohydrate (glucose or potatoes) were given; 3 to 4 hours later their usual breakfast was taken combined with lunch, and then their usual régime was resumed. Insulin was omitted the day prior to the test if the patient's usual injection-time had been in the evening, and in some experiments the patient remained without insulin for 48 hours preceding the test. On the test day the usual insulin dosage was given at either lunch or supper time, and in certain instances, as will appear in the tables, insulin was omitted on the day of the test.

The urine sugar was quantitated: 1, For the 24-hour period previous to the glucose test; 2, in the urine fractions obtained during the 3 or 4-hour period of the performance of the test; 3, in the urine collected from the end of the test until next morning and subsequently; 4, in the 24-hour periods during the 2 following days.

Estimations of the blood sugar were made to serve as controls.

The results in these 2 cases as well as in the remaining 7 appear to us to indicate a hitherto unrecognized aid in therapy. Table 1 shows that certain diabetics for whose treatment administration of insulin had previously been shown to be obligatory, are able to metabolize almost completely 100 gm. of glucose given fasting in the morning.

Patient K. T. excreted only 7 gm. of sugar on the day of the test, July 13th, as compared to 22 gm. on the preceding day. On July 24th the test was repeated, again with 100 gm. of glucose in 200 cc. of water, and only 13.5 gm. were excreted in the 24-hour urine for that day, although no insulin was taken. During the intervening period he had been on his usual régime as to diet and insulin. A similar result was obtained on August 7th despite the fact that

insulin had been omitted on the preceding day and his carbohydrate intake on the day of the test had been increased to 360 gm. In patient M. S. similar results were obtained on July 25th, although the additional 100 gm. of glucose were given 36 hours after his last dose of insulin.

TABLE 1.—INFLUENCE OF ONE ADDITIONAL DOSE OF GLUCOSE, 100 OR 50 GM., UPON THE CARBOHYDRATE BALANCE.

Date, 1939.	Time.	Blood sugar, mg. per 100 cc.	Urine.				Diet, gm. COH.	Insulin, P.Z. units.	COH metabolized.
			Vol., cc.	Sugar.					
				%.	Gm.	Gm. 24 hrs.			
Mr. K. T., aged 61, duration of diabetes 3 yrs.; 30 units insulin given in the morning before breakfast daily.									
July 12-13	8 A.M.-8 A.M.	...	2500	0.0	22.5	22.5	160	30	137.5
13	10.25 A.M.								
	(fasting)	83	135	0.0	0.0				
	10.30 A.M.	Given 100 gm. glucose in 250 cc. water							
	11 A.M.	250	26	0.0	0.0		100		
	11.30 A.M.	272	36	0.1	0.2				
	12.30 P.M.	278	105	3.3	3.4				
	1.30 P.M.	266	66	2.3	1.5	(30 PZI and breakfast with lunch)			
13-14	1.30 P.M.-8 A.M.		2000	0.1	2.0	7.0	160	30	253.0
14-15	...	..	1200	0.1	1.2	1.2	160	30	159.0
15-16	...	..		No specimen saved			160	30	
16-17	...	..	1000	0.0	0.0	0.0	160	30	160.0
17	10.10 A.M.								
	(fasting)	66	86	0.0	0.0				
	10.15 A.M.	Given 50 gm. glucose in 250 cc. water							
	10.45 A.M.	180	33	0.0	0.0		50		
	11.15 A.M.	205	25	1.6	0.4				
	12.15 P.M.	173	135	0.1	0.1				
	1.15 P.M.	150	82	0.0	0.0	(30 PZI and breakfast with lunch)			
17-18	1.30 P.M.-8 A.M.		1420	0.0	0.0	0.5	160	30	209.5
18-19	...	..	2000	0.0	0.0	0.0	160	30	160.0
19-20	...	..	1350	0.0	0.0	0.0	160	30	160.0
23-24	...	..	2500	0.0	0.0	0.0	160	30	160.0
24	7.30 A.M. (fasting).	The patient was given 100 gm. glucose in 250 cc. water. At 12.15 P.M. combined breakfast and lunch. Supper as usual.							
24-25	...	..	2250	0.6		13.5	260	0	246.5
25-26	...	..	2000	0.6		12.0	160	30	148.0
26-27	...	..	2500	0.0		0.0	160	30	160.0
Aug. 6	...	..	..	..		..	260	0	260.0
6-7	...	..	1100	0.0		0.0			
7	7.30 A.M. (fasting).	100 gm. glucose (48 hrs. after insulin.) At 12.15 P.M. insulin and breakfast with lunch. Supper as usual.							
7-8	...	..	960	1.2		11.5	360	30	348.5
8-9	...	..	2000	0.0		0.0	260	30	260.0
9-10	...	..	1680	0.0		9.0	260	30	260.0
Mr. M. S., aged 59, duration of diabetes 16 yrs.; 20 units insulin given at 6 P.M. daily. Last injection before test, July 23.									
July 24-25	8 A.M.-8 A.M.	..	2000	0.0	0.0	0.0	145	0	145.0
25	10.10 A.M.								
	(fasting)	112							
	10.15 A.M.	100 gm. glucose in 250 cc. water							
	10.45 A.M.	188	57	0.0	0.0		100		
	11.15 A.M.	234	36	0.1					
	12.15 P.M.	316	42	1.7	0.7				
	1.15 P.M.	345	87	2.5	2.2		Breakfast with lunch		
25-26	1.15 P.M.-8 A.M.		1500	0.2	2.5	5.4	145	20	239.5
26-27	...	..	2000	0.1	1.0	1.0	145	20	144.0
27-28	...	..	2000	0.0	0.0	0.0	145	20	145.0

The glucose tolerance test performed in patient K. T. on July 17th shows that when 50 gm. instead of 100 gm. of glucose were given in

the same amount of water the percentage of glucose retained was practically the same, hence the amount retained is not dependent upon the concentration of the sugar taken, under the conditions of the test.

Moreover, this carbohydrate retention was effected despite the fact that both patients had shown typically diabetic blood sugar curves.

Having observed their reaction to pure glucose, we then repeated the tests with 100 gm. of carbohydrate in the form of 500 gm. of potatoes, and as shown in Table 2 the results were quite similar as when glucose as such was given.

TABLE 2.—INFLUENCE OF ONE ADDITIONAL DOSE OF 500 GM. POTATOES UPON THE CARBOHYDRATE BALANCE.

Date, 1939,	Time.	Blood sugar, mg. per 100 cc.	Urine.				Diet, gm. COH.	Insulin, P.Z. units.	COH metab- olized.
			Vol., cc.	Sugar.		Gm. 24 hrs.			
				%.	Gm.				
Mr. K. T.*									
July 19-20	8 A.M.-8 A.M.	..	1350	0.0	0.0	0.0	160	30	160.0
20	9.30 A.M. (fasting)	77.3	63	0.0	0.0				
	9.45 A.M. to 9.50 A.M.	Ingestion of 500 gm. potatoes and 250 cc. water					100		
	10.20 A.M.	225.4	31	0.0	0.0				
	10.50 A.M.	280.2	30	1.6	0.5				
	11.50 A.M.	204.0	68	1.5	1.0		At 2 P.M. 30 PZI and breakfast with lunch		
	12.50 P.M.	138.8	55	0.53	0.3				
	1.50 P.M.	98.7	47	0.0	0.0				
20-21	1.50 P.M.-8 A.M.	..	3000	0.1	3.0		160	30	255.0
21-22	...	..	2500	0.44		11.0	160	30	149.0
22-23	...	..	2000	0.0	0.0	0.0	160	30	160.0
23-24	...	..	2500	0.0	0.0	0.0	160	30	160.0
Mr. M. S.*									
July 28	Diet as usual, no insulin.								
28-29	...	..	1500	0.1					
29	7.30 A.M.	The patient was given 500 gm. potatoes with 250 cc. water.				100			
	8 A.M.	..	32	0.1					
	8.30 A.M.	..	45	0.4	0.2				
	9.30 A.M.	..	46	1.7	0.8		Breakfast at 11 A.M., lunch at 1 P.M., supper at 6 P.M. Insulin in the evening		
	10.30 A.M.	..	60	1.2	0.7				
	11.30 A.M.	..	83	0.1	0.1				
	1 P.M.	..	51	0.3	0.2				
	6 P.M.	..	330	0.2	0.6				
	9 P.M.	..	197	0.2	0.4				
29-30	9 P.M.-7.30 A.M.	..	1000	0.0	0.0	3.0	145	20	242.0
30-31	...	..	2200	0.0	0.0	0.0	145	20	145.0
31- Aug. 1	...	..	1400	0.3		4.2	145	0	141.0
1	7.30 A.M.	500 gm. potatoes with 250 cc. water.				Diet and insulin as on July 29.			
1-2	...	..	1920	0.56		10.8	245	20	239.0
2	No insulin. Diet as usual.								
2-3	...	..	1440	0.4		5.8	145	0	139.0

\* Same patient as in Table 1.

These patients were under daily observation for periods of 28 and 15 days respectively. In addition to their ability to retain the extra sugar on each test day, their carbohydrate tolerance had been considerably raised by the end of the period, apparently under the influence of the additional carbohydrate in their daily diets (Table 3).



TABLE 3.—INFLUENCE OF DAILY ADDITION OF 500 GM. POTATOES UPON THE GENERAL CARBOHYDRATE TOLERANCE.

Date, 1939.	Time.	Urine.			Diet, gm. COH.	Insulin, P.Z. units.	COH metab- olized.
		Vol. cc.	%.	Sugar. Gm.			
Mr. K. T.*		2500	0.0	0.0	160	30	160
July 26-27	24-hr. period	2000	0.0	0.0	260†	30	260
27-28	24-hr. period	2000	0.2	4.0	260†	30	256
28-29	24-hr. period	2250	0.4	9.0	260†	30	251
29-30	24-hr. period	2500	0.0	0.0	260†	30	260
30-31	24-hr. period	2400	0.2	4.8	260†	0	255
Aug. 1	24-hr. period					0	139
1-2						0	235
Mr. M. S.*				Diet as usual, no insulin	145	20	239
Aug. 2	24-hr. period	1440	0.4	5.8	245†	20	235
2-3	24-hr. period	1440	0.7	10.0	245†	20	237
3-4	24-hr. period	1920	0.3	5.8	245†	20	243
4-5	24-hr. period	1440	0.7	10.0	245†	20	
5-6	24-hr. period	1920	0.4	7.7	245†	20	
6-7	24-hr. period	2200	0.1	2.0	245†	20	
7-8	24-hr. period						

\* Same patient as in Table 1.

† 250 gm. potatoes added both to lunch and supper.

During the 24 hours preceding the beginning of the tests on K. T. he excreted 22.5 gm. of dextrose in the urine, whereas after having been given the extra glucose in the morning of the first test his glucosuria diminished and was 0 on the third day, without modification of diet or of insulin dosage. During the subsequent 10 days the test with extra glucose was repeated 3 times and it was then found that he could be maintained without glucosuria on 260 gm. carbohydrate as against his former allowance of 160 gm. insulin remaining the same.

Towards the end of the observation period patient K. T. volunteered the information that he no longer had the feeling of constant fatigue of which he had complained for several years.

The other patient, S. M. (Table 2), reacted equally well to the ingestion of additional 100 gm. carbohydrate in the form of potatoes, and his carbohydrate tolerance was favorably influenced as well (Table 3).

It should be recalled, as previously stated that for at least several weeks preceding our observation periods both these men were at the limit of their carbohydrate tolerance, if not actually in negative carbohydrate balance.

Similar results were obtained with 7 other diabetics (Table 4). Three of these patients had a 2 to 3 plus reaction in the urine for acetone. For from 2 to 4 weeks preceding the test all 7 had been taking a standard diet containing either 100 or 150 gm. of carbohydrate. Four patients had not as yet received insulin, the other 3 had been taking either 20 or 35 units of regular insulin daily. Their ages ranged from 23 to 55 years. Glycosuria was present

in all and the amount of dextrose they excreted in 24 hours amounted to from 8 to 46 gm.

TABLE 4.—INFLUENCE OF ONE ADDITIONAL DOSE OF 50 GM. GLUCOSE UPON THE CARBOHYDRATE BALANCE IN 7 PATIENTS.

	Case No.:	1.	2.	3.†	4.	5.*†	6.††	7.*
24 hrs. urine before the test . . . . .	10	16.0	14.0	8.0	21	29.0	46.0	
First day. First 4 hrs. after glucose . . . . .	2	1.8	2.5	2.5	4	3.0	5.6	
First day. Remaining 20 hrs. . . . .	0	2.0	0.0	1.0	1	1.7	4.0	
Second day . . . . .	0	0.5	0.0	8.0	1	1.0	5.0	
Third day . . . . .	0	0.0	0.0	0.0	0	0.0	0.0	
Total 3 day excretion after glucose . . . . .	2	4.3	2.5	11.5	6	5.7	14.6	

\* 20 units regular insulin daily.

† 35 units regular insulin daily.

‡ 2 to 3 plus reaction for acetone.

The glucose tolerance test was performed by giving 50 gm. of glucose in 200 cc. of water in the morning, fasting. Four hours later the usual diet and insulin, if it had been given, were resumed. In 2 patients (Cases 1 and 3), the urine during the first 4 hours following the glucose contained about 2 gm. of sugar, but remained practically sugar-free during the remainder of the test day as well as on the 2 following days. The 5 other cases excreted up to almost 10 gm. on the test day and 2 of them (Cases 4 and 7), 5 and 8 gm. respectively, on the second day. Hence it is obvious that they retained from 71% to 96% of the 50 gm. of added glucose, a surprisingly high retention when it is remembered that in no case was the urine sugar-free previous to the test.

Repeated carbohydrate tolerance tests employing glucose or potatoes showed that certain diabetics who seemed to be at the limit of their carbohydrate tolerance, can tolerate and to their advantage a considerable additional amount of carbohydrate without added insulin.

TABLE 5.—INFLUENCE OF ADDITIONAL 50 GM. OF GLUCOSE UPON THE URINARY SUGAR IN LABILE SEVERE DIABETES.

Miss A. B., aged 32, duration of diabetes 18 yrs.

Aug. 11, 1939, sugar-free on 70 units and 190 gm. carbohydrate.

Aug. 12 no insulin.

Time.	Cc.	Urine.	
		Sugar.	
		%.	Gm.
7.15 A.M. . . . .	660	0.0	0.0
7.40 A.M. 50 gm. glucose in 300 cc. water . . . . .		:	
8.15 A.M. . . . .	180	2.0	3.6
9.00 A.M. . . . .	180	6.0	10.8
9.35 A.M. . . . .	120	10.0	12.0
10.00 A.M. . . . .	90	7.0	6.3
11.00 A.M. . . . .	270	10.0	27.0
11.45 A.M. . . . .	280	9.0	25.2
	1120		84.9

12.35 P.M. Blood sugar 515 mg. per 100 cc.

A relatively small group within the total diabetic population is represented by those cases, usually severe, which have the juvenile, highly reactive form of the disease. In them the glucose tolerance test results in the rapid excretion of all the test glucose and often of additional glucose of endogenous origin as well. A case in point is that of Miss A. B., and her reaction to the test is shown in Table 5. Such cases will obviously be unable to utilize additional carbohydrate unless their insulin dosage is proportionately increased.

**Conclusions.** 1. We recognize the great value of the glucose tolerance test as usually performed. However, the examination of the urine during the 3 days following the test appears to be even more useful in determining the *actual carbohydrate tolerance*. In the cases reported the usual tests would have indicated either more insulin or less carbohydrate, though further examinations as described showed that neither step was indicated.

2. Two of our cases examined over several weeks showed subjective and objective clinical improvement. Thus it would seem that our procedure could be employed to advantage where more carbohydrate is desirable but more insulin is contraindicated. A simple glucose tolerance test without blood sugar estimations but with recordings of the 24-hour urinary glucose over a period of several days before and after the test will indicate whether a given case can utilize additional carbohydrate.

We believe that many diabetics would benefit from the procedure herein described.

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## THE INCIDENCE OF NEUROPATHY IN PELLAGRA.

### THE EFFECT OF COCARBOXYLASE UPON ITS NEUROLOGIC SIGNS.\*

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THE trend in modern medicine toward explaining a disease syndrome on the basis of a single causative agent has led some to think that all symptoms of pellagrins arise from a deficiency of a single chemical substance, namely nicotinic acid amide. Recent progress in nutritional research indicates that a deprivation of nicotinic acid is not responsible for all the symptoms in human beings with pellagra. Spies and his coworkers,<sup>9-11</sup> Jolliffe,<sup>5</sup> Ruffin

\* This study was aided by grants from The Rockefeller Foundation, the Eli Lilly Company, and Anheuser-Busch, Inc.

and Smith,<sup>7</sup> Sebrell<sup>8</sup> *et al.* have shown, however, that pellagrins have associated deficiency of a number of nutritional elements. While treating pellagrins with nicotinic acid they observed that the alimentary tract symptoms, skin lesions, and many of the "neurasthenic" complaints were relieved, whereas there was no improvement in the pain of the calves, numbness of the extremities, weakness, difficulty in walking, dizziness, lassitude, fatigue, increase of sensitivity to light and noise, loss of memory, sleeplessness and general irritability. The administration of thiamin was followed by relief of many of these neuropathic signs and symptoms. Nevertheless, many patients who improved following treatment with nicotinic acid and thiamin, developed lesions characteristic of riboflavin deficiency. These lesions disappeared following the administration of adequate amounts of riboflavin.

In order to have some idea of the incidence of neuropathy among pellagrins, a group of patients in the Nutrition Clinic of the Hillman Hospital were examined carefully by special methods. This group of 50 white pellagrins consisted of 30 women and 16 men between the ages of 18 and 66 years, and 4 children between the ages of 8 and 13 years. The mean age of the adults was  $41.1 \pm 12.6$  years.\* Although they had been treated with nicotinic acid and riboflavin with considerable success, they had continued to eat a grossly inadequate diet and were chronically malnourished.

The 50 patients were grouped arbitrarily according to the severity of their pellagra: Group I (mild), 16 patients; Group II (moderately severe), 23 patients; Group III (severe), 10 patients. The remaining patient was so severely ill that he was not included in any of the above groups. Thus, more than three-quarters of all the patients were regarded as mild or moderately severe cases. The preponderance of such cases is explained by the fact that only ambulatory patients, many of whom lived distances up to one hundred miles from the clinic, were examined.

**Neurologic Signs and Symptoms.** The incidence and type of pathologic findings encountered in the neurologic examinations are shown in Chart 1. Signs pointing to disease of the peripheral nerves were prevalent, although the cranial nerves and central nervous system were involved occasionally.

In Groups I and II, practically three-quarters of the patients had tenderness of nerve trunks and abnormal electrical irritability of the motor nerves. About one-third showed a decrease of pain sensitivity and of pupillary reflexes, as well as ataxia. Less than one-fifth had decreased corneal reflexes, diminished muscle power, some diminution of touch sensation, pyramidal signs, nystagmus, deviation of the tongue, extrapyramidal signs or Romberg's signs, in descending order of frequency.

\* The first figure of the symbol expressed in this manner indicates in this paper always the mean, the second figure the standard deviation from the mean.

The 10 severe cases in Group III and the 1 very severe case each showed abnormal electrical irritability of the motor nerves. Three-quarters of these patients had tenderness of nerve trunks and decreased pain sensation. Approximately two-thirds had ataxia, while absent or decreased tendon reflexes were found in about two-fifths of the cases. About one-third had tremor, decrease in motor power, deviation of the tongue, and decreased corneal reflexes. Approximately one-quarter showed a positive Romberg test and one-fifth pyramidal signs.

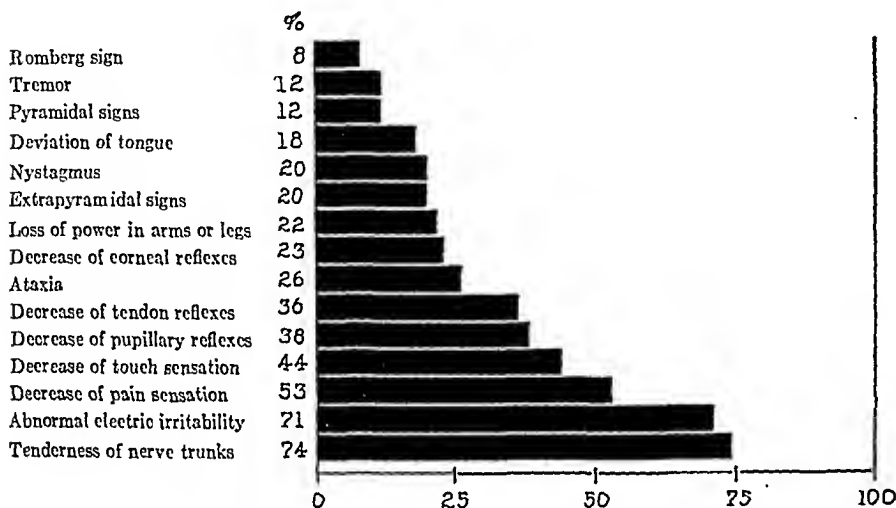


CHART 1.—Frequency histogram of nervous disturbances expressed in percentages of examination of 50 pellagrins.

Decreased pupillary and corneal reflexes, and absent or decreased tendon reflexes, as well as tenderness of nerve trunks, were found with about the same frequency in the group of the mild cases as in the severe cases. Partial loss of motor power, decrease of pain sensation, or evidence of pyramidal dysfunction were signs that were twice as common in the severe group. Nystagmus, decrease of touch sensation and extrapyramidal signs were found three times as often in the severe group. Ataxia was four times, tremor seven times, and Romberg's sign ten times more frequent in the group of severe cases, than in the less severe groups.

In 2 persons who complained of black spots before the eyes, para-central *scotomas* could be demonstrated in the visual fields between 5° and 10°.

In the majority of the patients the *pupils* were wide, being between 6 and 8 mm. in diameter. Mild differences in the size of the two pupils and irregularities of outline were not uncommon findings. The light reflexes were definitely impaired. Measurements of this reaction were made with the Hess-Zeiss pupilloscope.<sup>1</sup> The mean difference of intensity of light required to elicit pupillary contractions in these patients was  $9.4 \pm 4.1\%$ , whereas it was  $4.4 \pm 0.8$  in

a control group. The amount of increase in light intensity necessary before the recognition of the change was visually noted was 8.1% in the pellagra group, in contrast to 5% in the control group.

The *corneal reflex* was elicited in the group of pellagrins by a graded jet of air of  $0.77 \pm 0.41$  mg./mm<sup>2</sup>, compared with  $0.42 \pm 0.19$  normally required. The subjective sensitivity of the cornea, examined by graded hairs, was found to be  $2.15 \pm 0.48$  gm./mm<sup>2</sup>. in the average of 20 pellagrins, in contrast to  $1.2 \pm 0.2$  found in a large number of controls of middle age.

A highly significant association\* was found between the decrease of the pupillary reflex and abnormal electrical irritability of the peripheral nerves, and also between the decrease of corneal sensitivity and the decrease of pain sensitivity in the extremities. The former observation suggests that the disturbance of the pupillary reflex may be due to involvement of the motor side of the arc, the oculomotor nerve. The statistical relationship between the reduction of the corneal reflex and the decrease in the appreciation of pain in the extremities is interesting because of the fact that the sensory nerve endings in the cornea are essentially of the pain type.

In these pellagrins involvement of the *peripheral nerves* of the extremities was the commonest neurologic affection. The sensory and motor branches were diseased to approximately the same degree. The nerve trunks most frequently *tender* to pressure were the radial, ulnar, occipital, supraorbital and infraorbital nerves. In about one-half of the 50 pellagrins the muscles, especially those of the calves, were tender to deep pressure, and most of the patients complained spontaneously of soreness or pain in these muscles.

*Hypalgesia and hypesthesia* were usually of the glove and stocking type. A mean pressure of about 16 gm. (less than 1 gm. is required in the normal individual) had to be applied to a pin to elicit a "sharp" sensation in these pellagrins. In some of the patients a pressure of 40 gm. was not appreciated as sharp. Sometimes the hypalgesia was more marked in the skin distribution of one nerve, particularly the peroneal nerve. The mean pressure necessary to elicit a "touch" sensation in those showing diminution of this modality was 11 gm./mm.<sup>2</sup> (normally 1 gm.). Despite this finding, numbness in the legs and arms was a complaint in only a small number of patients. The appreciation of vibration was diminished in some instances, the appreciation of passive changes of position of the fingers and toes was always normal.

\* The probability that a significant relationship exists between the occurrence of the two signs or symptoms in the whole group examined is estimated statistically by the chi square test. If the probability that the result is produced by chance is 5% or less, the result is taken to be "significant"; if 1% or less, to be "highly significant."

The question whether the change in the pupillary reflexes observed in some of the patients after co-carboxylase treatment (see later) represents a significant improvement or is due to chance was examined by the "t-test." This test expresses the quotient of the difference between the mean of the pupillary reflexes of various patients before and after treatment, divided by its standard error.<sup>2</sup>

*Ataxia* and "past-pointing" in the finger-to-nose and the heel-to-knee tests appeared to be significantly associated with involvement of the motor nerves and not with loss of sensitivity. A positive Romberg sign could not be associated statistically with a disturbance in the peripheral nerves, but appeared to be of central origin. The same was true of tremor of head and arms at rest.

The *strength-duration curves* of three muscle groups were examined in all patients, namely, the common finger extensor, the superficial finger flexor, and the long peroneal muscle. At least one of these muscles gave pathologic reactions in 71% of these patients. The peroneal muscle group was most frequently involved (81%), with the finger flexor next (68.5%), and the finger extensors last (30.4%). The majority of the patients showed a mild degree of underexcitability, a small number showed severe underexcitability, with spontaneous fasciculation and reversal of the polar formula; a few patients showed overexcitability. The figures for the peroneal group in terms of chronaxy were  $105 \pm 29.5$  volts,  $1.09 \pm 0.49$  msec., against a normal mean of  $105 \pm 7.5$  volts,  $0.3 \pm 0.05$  msec.; in terms of microcoulombs  $90 \pm 10.2$  against a normal mean of  $20.1 \pm 0.6$ .\*

There have been criticisms of the theory of chronaximetric measurement which need not be considered here. The important point for work of this kind is whether or not there is a relationship between electrical irritability of the nerve-muscle apparatus and degree of neuropathy as determined by neurologic examination, and whether or not the strength-duration curve returns to its normal slope as therapy restores the nerve function.<sup>6</sup>

Five out of 50 persons showed a mild *Parkinsonism*. None of these patients had a history of encephalitis. Bean and Spies have given intravenously 50 mg. synthetic vitamin B<sub>6</sub> to 10 more cases of Parkinsonism of at least 4 years' duration. In a few minutes the symptoms disappeared in 2 cases and greatly decreased in 3 others. No improvement occurred in 5.

**The Effect of Cocarboxylase on the Neurologic Signs of Pellagrins.** The possibility of neurologic, psychiatric and biochemical studies provided a propitious opportunity for conducting a therapeutic test on a limited number of pellagrins. The results of the neurologic studies are recorded here and correlated with the chemical findings, but the detail accounts of the psychiatric and chemical results will be reported separately.<sup>3,4</sup>

Nine pellagrins who, in previous months, had been treated with nicotinic acid continued to have symptoms related to the peripheral nerves. Some of these patients showed, in addition, signs of central nervous system involvement. These selected patients were examined neurologically, psychiatrically and chemically several times

\* Microcoulomb is the product of the voltage times microfarads or time in milliseconds. For technical reasons the actual figures are given as the square root of microcoulombs ( $\sqrt{\mu C}$ ). The normal values for the various muscle groups are given in the heading of Table 1.

before and after the intravenous injection of 50 mg. and more of synthetic cocarboxylase (the phosphorulated ester of thiamin).<sup>\*</sup> Seven of these 9 persons showed a dramatic improvement following the cocarboxylase injection.

**OBSERVATIONS.** The motor *pupillary reflex* showed a significant improvement after the injection of cocarboxylase in 3 of 9 persons. The light difference could be reduced, *e. g.*, from 9.2% before, to 4.4% after treatment. In 4 persons the reflex was normal, and in 1 it was decreased before, and did not recover after cocarboxylase. The visual light intensity discrimination which was decreased in 3 persons returned to normal, that is from 6.3% to 2.9%, in 2 persons following treatment.

The *corneal reflex* which had been decreased in 3 patients improved by about 64% (from 1.21 to 0.54 mg./mm.<sup>2</sup>—normally 0.42) in 1. In 2 persons the corneal reflex remained unchanged following treatment. The subjective sensitivity of the cornea did not change to a significant degree.

A paracentral *scotoma* present in 1 patient disappeared within 6 hours after a single treatment but returned 12 hours later.

*Nystagmus* present in 4 persons disappeared in 1. The strength of the *grip* increased in 2 persons. The *tendon reflexes* improved moderately in 1 of the 3 persons who had decreased tendon reflexes. *Ataxia* improved or disappeared in 3 of 4 cases so affected. *Tenderness* of the nerve trunks improved in 4 of the 6 cases in which tenderness was present. Touch and pain *sensitivity* improved in 5 of the 6 cases thus affected, in some instances becoming normal.

The *electrical excitability* changed from underexcitability or overirritability to normal in one or more of the muscles tested in all but 1 patient. In several instances it progressed from underexcitability to overirritability, and then relapsed to its previous state of underexcitability after some days.

Table 1 may serve as an example of these observations.

In this person a single intravenous injection of 50 mg. of cocarboxylase was followed within 1 hour by return to normal of the electrical muscle reaction. The improvement went on to overexcitability in the flexor for 4 days. At the same time clinical neurologic symptoms and signs as well as psychoneurotic complaints and blood chemistry—bisulphite binding substances (BBS), including pyruvates,<sup>14</sup> and the arterio-venous oxygen difference—improved or returned to normal.

On the fifth day after the injection, the peroneal muscles relapsed and became underexcitable, and subjective and objective signs of neuropathy again became manifest.

The striking feature in this group of patients was the rapidity with which improvement followed the administration of cocarboxylase at intervals of from 1 to 4 hours, the parallelism between the

\* Furnished through the courtesy of Merck & Co., Rahway, N. J.



TABLE 1.—PROTOCOL OF ONE OF THE NINE THERAPEUTIC STUDIES IN PELLAGRINS.

Date.	Units:	Electrical irritability in microeoulombs ( $\sqrt{\mu C}$ ) of finger extens. near m.			O <sub>2</sub> consumption of the brain.	Bisulph. binding subst.	Cozymase.	Pupil reflex		Sensitivity to touch.		Neurologic symptoms and signs.
		$\sqrt{\mu C}$	$\sqrt{\mu C}$	$\sqrt{\mu C}$				mot.	%	gm./mm. <sup>2</sup>	gm.	
6/19	Normal:	6-9	3-6	3-6	7.43+	1-	53		5.3	1	1	Pupillary reflex diminished. Nystagmus. Tremor and ataxia. Loss of touch sensation in legs. Tenderness of nerve trunks.
	Time.											
	10:00	8.7	6.3	9.1	1.35	3.25	13	7.5	5.3	4-15		
6/20	11:50											Pupillary reflexes normal and light discrimination further improved.
				50 mg. Cocarboxylase								
	1:00			5.9								
	3:15			4.0	2.61	1.05	13	5.3	2.4			
6/20	10:00	8.9	4.2	5.8								Sensitivity in legs normal. No tenderness of nerve trunks. Flexor overexcitable.
	2:00	8.2	5.8	5.8								
6/21	2:00	8.5	2.0	4.1						1	1	Feels fine. No complaints.
6/22	3:00	8.5	2.0	5.2								Headache and pain in back of neck. Left arm heavy and aching. Nerve trunks again tender to pressure.
6/24	3:00	8.5	2.5	7.7				7.2	4.4			Relapsing.
6/26	11:00	7.4	3.5	7.5	6.20	1.37	26					

The figures show the influence of a single intravenous injection of 50 mg. cocarboxylase on the electrical irritability of three muscle groups in terms of  $\sqrt{\mu C}$ ; on brain respiration in terms of the arterio-venous oxygen difference in the cerebral blood; the amount of bisulphite binding substances in the peripheral venous blood determined by Kimwiche *et al.*; on the cozymase content of the whole blood determined with the influenza bacilli growth method according to the technique of Vilter *et al.*; on pupillary reflexes and visual discriminatory acuity; on touch and pain sensitivity measured with v. Frey's hairs and thorns; on the clinical neurologic signs and symptoms. Italics indicate pathologic values.

clinical and chemical findings, and the relapse a number of days after the injection.

*Studies with Riboflavin and Vitamin B<sub>6</sub>.* The intravenous injection of 100 mg. of riboflavin in 2 persons with neurologic signs and symptoms similar to those of the patient described above, effected no demonstrable change in the neurologic picture.

The intravenous injection of 100 mg. of vitamin B<sub>6</sub> in 4 pellagrins not treated previously with thiamin or riboflavin was followed in 2 by an increase in severity of the pathologic signs of peripheral and central nervous system for the duration of 2 days. The electrical excitability showed a tendency to become increasingly abnormal. The oxygen consumption of the brain measured by arterio-venous oxygen difference decreased after the administration of vitamin B<sub>6</sub>. Some patients became sleepy and drowsy.

**Discussion.** The discrepancy between the well-known experiment in which the paralyzed, vitamin B<sub>1</sub>-deficient pigeon recovers almost immediately after an injection of thiamin, and the experience that thiamin deficiency is followed by the degenerative process of neuropathy (neuritis) has been the subject of some discussion in the literature. Our study demonstrates that the underexcitable nerve-muscle apparatus may be restored to normal excitability within from 1 to 4 hours after a single injection of 50 mg. cocarboxylase. This finding indicates that a great number of nerve fibers were anatomically intact, but unable to act properly, as the result of altered metabolism. This deduction is corroborated by the observation that the nerve-muscle mechanism readily returns to its improperly functioning state a few days after the improvement induced by cocarboxylase has occurred if the person remains on a diet deficient in B<sub>1</sub>. Some of the muscles in the patients remained underexcitable which probably indicates that too many of their nerve fibers were anatomically damaged.

Two patients failed to show the same improvement on the amount of cocarboxylase which improved the signs and symptoms of the other cases. This result may indicate that some individuals ultimately reach a stage when the changes in the nervous system are not readily reversible.

It may be well to indicate here that the neuropathy associated with the average endemic pellagrin (in the South), cannot be compared to the severe form of neuropathy which is seen in most clinics in association with long-standing alcoholic addiction.

The result of the determination of thiamin excretion\* in the urine of these patients points in the same direction. This investigation which was performed by Dr. L. Jonas of the Hospital of the Univer-

\* For the chemical determination of thiamin in the urine the method of Westenberg and Goudsmit<sup>13</sup> was used in the modification of J. K. Cline. The thiochrome used as color standard was supplied by Merck & Co., Rahway, N. J.

sity of Pennsylvania, suggests that those patients who showed the best clinical and chemical improvement following cocarboxylase administration retained most of the injected cocarboxylase, while those with little or no improvement excreted most of it in the urine.

In patients who showed no improvement in electrical muscle irritability or clinical neurologic signs, the B.B.S. (bisulphite binding substance) values continued high, while they decreased simultaneously with electrical and clinical improvement. This suggests that an association exists between these two factors.

The continuous effect of a single intravenous dose of 50 mg. of cocarboxylase over a period of 3 or 4 days intimates that this amount is sufficient not only to produce the immediate beneficial effect upon the nerves, but also to sustain it to a certain degree for a limited time.

The clinical syndrome described in the older literature as pellagra is in reality a complex caused by a deficiency of various nutritional factors, among which the lack of vitamin B<sub>1</sub> is important. In most of our patients the thiamin deficiency, despite the chronicity of the condition, had not yet passed the stage of disease in which the neuropathy could be cured by thiamin administration.

**Summary.** 1. Clinical examination of 50 pellagrins revealed that 75% had polyneuropathy of the motor and sensory nerves; 20% had extrapyramidal signs, of which one-half showed mild Parkinsonism; 12.5% had tremor and pyramidal tract signs.

2. Intravenous administration of 50 mg. or more of phosphorylated thiamin (cocarboxylase) to 9 of these pellagrins was followed in 7 instances by quantitative improvement in the electrical irritability of a number of muscles, in the pupillary and corneal reflexes and in the sensitivity to touch and pinprick. These indices often became normal within 1 to 4 hours after injection, and improvement was maintained from 1 to 5 days. The patient then tended to regress and eventually returned to the condition preceding treatment.

3. The clinical effect of cocarboxylase was found to be identical with that of thiamin (vitamin B<sub>1</sub>) which had been studied previously.

4. The chemical changes in the blood paralleled the clinical neurologic improvement following administration of cocarboxylase.

5. These observations confirmed our premise that the neuropathy which is common among pellagrins is caused by a deficiency of vitamin B<sub>1</sub>.

6. Patients who retained most of the injected cocarboxylase improved readily, while those who were unable to retain it, showed little or no improvement.

7. The administration of synthetic riboflavin was not followed by a change of the neurologic signs.

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## CEREBRAL CARBOHYDRATE METABOLISM DURING DEFICIENCY OF VARIOUS MEMBERS OF THE VITAMIN B COMPLEX.\*

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THERE is good evidence that various members of the vitamin B complex are involved in carbohydrate metabolism. In regard to B<sub>1</sub>, much of the data were obtained on tissues excised from avitaminotic animals.<sup>8</sup> The mechanism of action of other members of this group, riboflavin and nicotinic acid amide, has been studied mainly as isolated enzyme systems.<sup>11</sup> The present observations were made on patients who, in addition to pellagra (nicotinic acid amide deficiency), exhibited signs of inadequate ingestion of the other vitamins.<sup>9</sup> The cerebral metabolism of these patients was examined not only because pellagrins exhibiting severe forms of vitamin deficiencies develop mental changes<sup>3</sup> but also because the brain oxidizes carbohydrate chiefly. Thus, any alteration in carbohydrate metabolism resulting from a deficiency of this group of vitamins should be more readily observed in this organ than in others which are capable of oxidizing fat as well as carbohydrate.

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**Method.** Carbohydrate metabolism was studied by measuring the differences between oxygen,<sup>10</sup> glucose,<sup>4</sup> and lactic acid<sup>2</sup> of the femoral arterial blood and that of the internal jugular vein.<sup>7</sup> The femoral arterial sample is similar to that going to the brain while the internal jugular vein carries the return circulation from that organ. The arterial and venous blood samples were examined before and in most instances after specific treatment with vitamin B<sub>1</sub>, nicotinic acid amide, riboflavin, and vitamin B<sub>6</sub>.

**Results.** Forty-nine determinations of the cerebral exchange of blood gases and utilization of sugar and lactic acid were made on 27 patients. In order to save space only the averages are presented. The results reveal a cerebral oxygen utilization of  $6.12 \pm 0.21$  vol. % before specific therapy and of  $5.51 \pm 0.21$  vol. % after specific treatment. The difference is probably not significant. The A:V exchange for the entire series is  $5.82 \pm 0.15$  vol. %. The mean glucose utilization is 7.6 mg. per 100 cc. No difference is observed in the average lactic acid content of the arterial (16.9 mg. per 100 cc.) and venous (16 mg. per 100 cc.) blood. The oxygen capacity is lower than normal both before and after therapy, and the average is 15.3 vol. %, the normal being approximately 20 vol. %.

TABLE 1.—THE OXYGEN AND SUGAR CONTENTS OF THE ARTERIAL AND VENOUS CEREBRAL BLOOD BEFORE AND 3 HOURS AFTER THE INJECTION OF 50 MG. OF COCARBOXYLASE.\*

Patient No.	Arterial oxygen.		Venous oxygen content.	Diff.	Sugar.	
	Capacity.	Content.			Arterial.	Venous.
1	13.01	12.68	8.01	4.67	100	102
	13.97	13.87	9.15	4.72	88	78
2	15.95	14.50	10.58	3.92	103	93
	15.35	14.74	10.69	4.05	101	90
3	16.55	16.07	14.72	1.35	77	74
	16.57	16.62	13.01	2.61	124	118
4	16.89	16.54	10.41	6.13	109	101
	16.84	16.23	9.42	6.81	93	96
5	17.87	16.47	9.02	7.45	90	79
	18.14	16.19	11.87	4.32	70	66
6	13.63	13.01	6.89	6.12	92	75
	13.67	13.32	6.17	7.15	86	77
7	15.39	14.94	11.00	3.94	68	61
	15.24	14.49	11.07	3.42	132	127
8	16.93	16.08	11.61	4.47	56	50
	16.22	15.44	11.55	3.89	68	68
Average	15.77	15.01	10.32	4.69	91.1	84.7

(Normal 7.4)

*Vitamin B<sub>1</sub>.* Eight pellagrins with peripheral neuritis were examined before and at intervals after the intravenous injection of 50 mg. of cocarboxylase, phosphorylated B<sub>1</sub>.† This therapy produced improvements in 6 of the 8 patients. The average A:V oxygen difference is  $4.76 \pm 0.46$  vol. % before specific therapy and  $4.62 \pm$

\* Oxygen expressed as vol. %. Sugar expressed as mg. per 100 cc.

† These are the same patients as those described clinically in the preceding paper.

0.38 vol. % 3 hours after the medication. The average for both series is  $4.69 \pm 0.37$  vol. %. This value is low compared with an average A:V oxygen utilization of  $6.6 \pm 0.14$  in a group of pellagrins free of complicating vitamin deficiencies. What is more, the smallest oxygen utilization of any patient was observed in a pellagrin with an additional B<sub>1</sub> deficiency (Patient 3, Table 1) who exhibited A:V differences of 1.35 and 2.61 vol. % respectively before and 3 hours after administration of cocarboxylase. Pellagrins relatively free of complicating vitamin deficiencies had an average A:V oxygen uptake of  $6.16 \pm 0.14$ . The administration of nicotinic acid amide, riboflavin, and vitamin B<sub>6</sub> in 7, 3, and 3 patients respectively produced no significant change in the oxygen A:V differences of the brain. The average glucose utilization is 6.4 mg. per 100 cc.

**Discussion.** An analysis of the data discloses that the lowest oxygen utilization occurred in those pellagrins who also had beriberi as indicated by the neurologic finding given in the preceding paper. The latter exhibited an average value of 4.69 vol. %, as against 5.82 vol. % for the entire group. The average oxygen consumption of pellagrins relatively free of other vitamin deficiencies is 6.16 vol. %. A value of 7.43 vol. % has been observed\* for normal subjects. The difference between the last two values, 1.27 vol. %, though significant by Fisher's statistical method, is not large. This result, moreover, cannot be generalized because of the small number of pellagrins relatively free of other deficiencies. But there is a greater difference, 2.74 vol. %, between the normals and the pellagrins with complicating beriberi. Unless cerebral blood flow is simultaneously determined, however, no exact estimations may be made of the oxygen consumption of the brain. The small A:V oxygen utilization observed in pellagrins with a complicating beriberi may be due to a more rapid blood flow, approximately a 60% increase over the normal. The low oxygen capacity of the blood (the average of 15.77 vol. % is approximately  $\frac{3}{4}$  of the normal value) is not of sufficient degree to cause a more rapid blood flow. An increase would be necessary to accommodate for an anemia but in these observations the average oxygen content of the venous blood was 10.32 vol. %, an adequate reserve. Lennox,<sup>6</sup> moreover, showed that under a wide variety of conditions, blood flow through the brain is remarkably constant. A diminution of brain metabolism would therefore appear more likely. Such an interpretation is in accordance with Peters' observations of cerebral tissue of avitaminotic pigeons.

Correlated with a diminished oxygen uptake is the average glucose utilization of 6.4 mg. per 100 cc. In patients without vitamin deficiencies, average values of 14.6 mg. per 100 cc.\* have been observed. A decreased uptake of glucose is to be expected in an organ with

\* Unpublished data.

depressed metabolism, if it obtains its energy predominantly from the combustion of carbohydrate. In normals and patients with schizophrenia<sup>5a</sup> the utilization of glucose is greater than can be accounted for by the oxygen uptake. In the present observation, however, the utilization of oxygen and glucose approach stoichiometric proportions. The diminished cerebral metabolism may afford an explanation for the mental changes observed in these pellagrins with accompanying thiamin deficiency. A decline of brain metabolism has been found to produce mental changes.<sup>5b</sup>

That vitamin B<sub>1</sub> is necessary for the oxidation of a breakdown product of sugar, namely, pyruvic acid, has been demonstrated by Peters and others.<sup>8</sup> They noted a decreased oxygen usage in cerebral tissues excised from B<sub>1</sub> avitaminotic animals, a decrease reversible in the presence of cocarboxylase.<sup>1</sup> Such a reversal did not occur in the present experiments. This may be due to lack of time for restitution. In all cases the second blood samples were drawn only 3 hours after the injection of cocarboxylase. In one instance (Patient 3, Table 1), however, a third pair of samples collected 1 week later did disclose an increased cerebral metabolism.

It must also be remembered that the vitamins are closely interrelated in the oxidative processes. In our polyavitaminotic patients the replacement of only one of the missing essentials in this subgroup could not be expected to restore function of the enzyme system. Finally the low cerebral oxygen uptake may be caused by some other deficiency accompanying a lack of B<sub>1</sub>. In any case this low oxygen consumption demonstrates a central component of this disease, and may afford an explanation for the mental changes. No utilization of lactic acid was noted, which is in accordance with previous observations *in vivo*.<sup>5a</sup>

**Summary and Conclusions.** Forty-nine observations were made in 27 polyavitaminotic patients whose most outstanding deficiency disease was pellagra. Samples of blood entering and leaving the brain were examined for oxygen, sugar, and lactic acid. The average A:V differences for oxygen are 5.82 vol. % in this group, compared to 7.43 vol. % in normal subjects. For glucose, the average A:V difference was 7.6 mg. per 100 cc., compared to 14.6 mg. per 100 cc. in normal subjects. No difference is observed in the average lactic acid contents between arterial and venous blood.

A group of 7 pellagrins presenting a clinical picture relatively uncomplicated by other deficiency diseases revealed an oxygen A:V difference of 6.16 vol. %, somewhat lower than the normal.

However, in 8 individuals who had pellagra complicated by beriberi, a more marked depression of the oxygen A:V difference was observed with an average value of 4.69 vol. %. This difference may be caused either by a blood flow increased 60% over the normal or by a diminished cerebral metabolism. The latter possibility is regarded as more likely. If cerebral metabolism is decreased in

pellagra complicated by beriberi, it is difficult to determine whether the low oxygen uptake is due to lack of one vitamin or to a poly-avitaminosis. However, such observations may afford a basis for an explanation of the mental changes of this syndrome.

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### PORPHYRINURIA IN PELLAGRA.

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SINCE Ellinger and Dojmi<sup>10</sup> reported the finding of increased urinary porphyrin in 8 patients with pellagra, a number of reports have been published dealing with the porphyrinuria of pellagrins. Beekh, Ellinger and Spies<sup>2</sup> studied the output of a chromogenic material which they called "porphyrin" in the urine of 19 patients having pellagra, 14 of whom were inebriates. Their findings indicated that the "porphyrin"\* output was approximately related to the severity of the skin and mucous membrane lesions, and that the excretion returned to normal following treatment with diet, yeast and liver, and coincident with regression of the disease. Spies and his coworkers<sup>19-21</sup> then noted that nicotinic acid causes a decrease in the excretion of chromogenic material not only in pellagrins, but in certain other diseases. The increased porphyrin excretion in pellagra and in certain congenital diseases of the skin, such as epidermolysis bullosa and hydroa vaeciniiforme, coupled with the increased photosensitivity observed in congenital porphyria, is interesting in view of the work of Smith and Ruffin<sup>18</sup> who found a

\* Bean, Vilter and Spies<sup>1</sup> have since designated their "porphyrin" as "ether soluble pigments which have the color of porphyrin in 25% hydrochloric acid."



correlation between exposure to sunlight and the development of the cutaneous lesions of pellagra. Recent studies of porphyrin excretion, however, seem to indicate that it is usually associated with disturbances of the general health, and that photosensitivity or skin lesions have no direct relation to the porphyrinuria.<sup>6</sup>

Porphyrinuria occurs in many pathologic conditions such as plumbism, sulfanilamide poisoning, pigment cirrhosis of the liver, pernicious anemia, hemolytic jaundice, chronic alcoholism, arsenical poisoning, and congenital porphyria.<sup>24</sup> These conditions point to involvement of the liver, bone marrow, or reticulo-endothelial system. Many of the phenomena observed in pellagra, such as abdominal distress, diarrhea, pigmentation of the skin, and photosensitivity are often found in patients exhibiting acute toxic porphyria. Are these pellagrous symptoms due directly to toxic effects of excessive porphyrins or are the porphyrinuria and these symptoms alike manifestations of systemic involvement?

Several investigators have suggested that porphyrinuria may be an indication of hepatic insufficiency.<sup>7,25,21</sup> We, therefore, felt that the explanation of porphyrinuria in pellagra might be aided by a study of porphyrin excretion in conjunction with administration of nicotinic acid, changes in liver function, and disturbances in hematopoiesis.

**Methods.** The subjects in this study were 9 inebriates admitted to the Medical Service of the Psychiatric Division of this hospital who, at the time of admission, presented either a pellagrous stomatitis, dermatitis, or both. As a control, these patients were maintained for several days with a diet low in the vitamin B complex<sup>17</sup> supplemented by 5% glucose in physiologic saline in amounts sufficient to maintain an adequate caloric and fluid intake.<sup>16</sup> Following the control period, and while still maintaining the patient with the same regimen, nicotinic acid\* was administered, usually in amounts of 1000 mg. daily by mouth, in divided doses. After the first few days, when the patient exhibited marked improvement in his pellagra symptoms, the amount of nicotinic acid was reduced to a maintenance dose of from 100 to 500 mg. daily. At this time, too, the diet was usually changed to one having a high content of the B vitamins<sup>15</sup> with supplements of vegex† and thiamin.‡ Porphyrin determinations were made on 24-hour urine specimens collected in brown bottles, preserved with thymol and kept in an ice-box. In addition, the following tests were made by methods described in previous publications from this clinic:<sup>3,14a,b</sup> levulose tolerance, bromsulphalein retention, quantitative serum bilirubin, van den Bergh reaction, red blood cell count, white blood cell count, hemoglobin, mean corpuscular volume, maximum packing, corpuscular hemoglobin, and color index.

The determination of porphyrin was made by the method of Dobriner *et al.*<sup>8,9a</sup> which is based on the extraction of porphyrins (mainly coproporphyrin) with ether in the presence of glacial acetic acid and transference to dilute hydrochloric acid. Estimation of the porphyrin content of the hydrochloric acid extract was made by comparison of the fluorescence of

\* Supplied by Merck & Co., Rahway, N. J., and by S.M.A. Corporation, Chicago, Illinois.

† Supplied by Vegex, Incorporated, New York, N. Y.

‡ Supplied by Merck & Co., Rahway, N. J.

the unknown against hydrochloric acid solutions of known porphyrin content in a fluorimeter, using a mercury vapor lamp behind a Wood's filter to screen the visible light. The quantities and the kind of porphyrin extracted were confirmed spectroscopically by comparison against standard solutions with a hand spectroscope.

Only coproporphyrins I and III are extracted by this method. Such porphyrins as uroporphyrin, protoporphyrin, and others, are rarely found in any significant amounts in the urine, except in congenital porphyria, and, if present, are largely removed by this method. Recovery of added coproporphyrin by the above method was within 2%.

**Results.** Using the above procedure, the urinary porphyrin excretion of 7 normal subjects, consuming a good *ad lib.* diet, was found to range between 30 and 120 micrograms daily. These findings agree with those of Dobriner and his coworkers<sup>8,9a</sup> in 5 normal subjects, and are therefore not tabulated. Data on the 9 pellagrins are tabulated in Table 1.

Two subjects (Cases 3, 6) did not exhibit porphyrinuria at any time.

One subject (Case 1) exhibited porphyrinuria on the twenty-fourth day only, at a time when he had recovered from his pellagra following administration of nicotinic acid.

Six subjects (Cases 2, 4, 5, 7, 8, 9) had a definite porphyrinuria at some time during their hospital stay. In 3 (Cases 2, 7, 8) there seemed to be a definite correlation between the severity of the pellagra and the excretion of porphyrins, in that the porphyrinuria was high during the severe manifestations of the disease but decreased and returned to normal as the symptoms subsided. In 2 of these subjects (Cases 2, 7) improvement occurred spontaneously while they were maintained with the basal diet; in 1 (Case 8), the improvement promptly followed administration of nicotinic acid. In 3 (Cases 4, 5, 9) our data do not show any correlation between severity of pellagra and porphyrinuria. In one of these (Case 4) porphyrinuria increased as the pellagra disappeared with nicotinic acid treatment; in 1 (Case 9) transient porphyrinuria occurred during both the control period and following recovery; and in one (Case 5) only a single porphyrin determination was made.

All 6 subjects (Cases 2, 4, 5, 7, 8, 9) who exhibited porphyrinuria showed at some time during their hospital stay impaired liver function in the form of bilirubinemia, retention of bromsulphalein, or a positive levulose tolerance test. In 3 of these (Cases 4, 7, 9) one test was abnormal; in 1 (Case 2) two tests were abnormal; and in 2 (Cases 5, 8) all three tests were abnormal. In the 2 (Cases 3, 6) who did not exhibit porphyrinuria, none of these three liver function tests was abnormal. In the 1 (Case 1) who showed a porphyrinuria only on the twenty-fourth day, two of the tests were abnormal.

Blood studies were done in 6 subjects (Cases 1, 2, 4, 7, 8, 9), of whom 2 (Cases 7, 8) showed a quantitative anemia; both of these

TABLE 1.—SUMMARY OF THE DATA ON NINE PELLAGRINS.

Case.	Age.	Sex.	Day.	Stomatitis.	Dermatitis.	Diarrhea.	R.B.C., millions.	W.B.C.	Hb.	C.I.	Maximum packing.	M. C. V.	Corp. hb.	Serum bilirubin.	van den Bergh.	Lev. tol.	Bromsulph. retention.	Diet.	Therapy.	Porphyria excretion.
1	45	F	0 6 20 24	++ ++ ++ 0	+++ +++ +++ 0	0	4.91	7,450	14.2	0.99	40.5	80.4	28.9	.. 0.8	.. Neg.	+	20% 5%	P.P. " "	0 NiAc. "	25 50 30 130
2	51	M	0 5 6 8	++ ++ ++ 0	+++ +++ +++ +	0	5.08	11,900	13.5	0.92	40.5	79.7	26.5	1.32	Del.			P.P. " "	0 0 0 0	170 290 100
3	63	M	0 1 2	0	+++ +++ +	0	5.33	12,850	15.5	1.0	47.0	88.1	20.0	0.6	Neg.	N	0%	P.P. " "	0 0 0	10 5 5
4	36	M	0 1 4	++ ++ +	+++ +++ +	++ +	5.41	10,100	14.5	0.92	51.0	94.3	26.8	1.0	Neg.	+	0%	P.P. " "	0 NiAc.	0 155 190
5	55	M	0	++	+++	0								3.3	Imm.	+	10%	P.P.	0	170
6	68	M	0 6 8 11	++ ++ ++ +	+++ +++ +++ 0	0								1.0	Neg.	N	0%	P.P. " "	0 0 NiAc.	10 0 15 15 20
7	40	M	0 1 5 10	++ ++ ++ +	+++ +++ +++ +	0	3.84	5,050	11.5	1.03	38.0	98.9	29.9	1.6 1.1	Neg. Del.	N	0%	P.P. " "	0 0 0 NiAc.	205 5 10 30
8	29	F	0 1 2 4 14	++ ++ ++ ++ 0	0	+++ +++ +++ +	2.87		7.6	0.91		101.9	26.4	2.0	Del.			P.P. " "	0 0 NiAc.	320 300 315 90 20
9	45	M	0 2 10 17 21 23	++ ++ ++ ++ 0 0	+++ +++ +++ +++ 0 0	++ ++ ++ 0 0	4.11 3.78	13,350 9,150	10.8 10.0	0.91 0.91	36.0 33.0	87.6 82.4	26.3 26.1	0.53	Neg.	+	0%	P.P. " "	0 0 NiAc.	25 145 0 70 30 125
				0	0	0	4.78	10,600	13.5	0.97	40.0	83.8	28.3			+	0%	High B	0	

Severity of symptoms are graded from 0 to ++++. P.P. = diet deficient in the vitamin B complex. High B = diet with a high vitamin B content. Ni.Ac. = nicotinic acid. Excretion of porphyrins is expressed as micrograms in 24 hours.

exhibited porphyrinuria. Of the remaining 4 subjects, all having a normal blood picture, 3 (Cases 2, 4, 9) exhibited porphyrinuria. No apparent correlation, therefore, exists in our subjects between the blood picture and porphyrinuria.

**Discussion.** Our results indicate that porphyrinuria cannot be used either as a diagnostic criterion or as a therapeutic guide in pellagra. The experience of Sydenstricker<sup>23</sup> and Watson,<sup>25b</sup> who found that porphyrinuria was an inconstant factor in pellagra, is confirmed. Our findings indicate that porphyrinuria is present in about two-thirds of the pellagrins; but in only one-half of these can the porphyrinuria be correlated with the severity of the disease; in the other half, the porphyrinuria bears no relation to the stage or severity of the disease.

Based on their results in the treatment of porphyrinuria by nicotinic acid, Spies *et al.*<sup>19,21</sup> have suggested a possible connection between nicotinic acid and porphyrin metabolism. This is not substantiated by our studies since porphyrinuria may decrease without the administration of nicotinic acid, or increase following administration of nicotinic acid and while the manifestations of pellagra are regressing. These facts also indicate that the symptoms of pellagra are in no way dependent on impaired porphyrin metabolism as manifested by increased porphyrinuria.

There is no evidence in any of our hematologic studies of a disturbed bone marrow activity with consequent alterations in hematopoiesis to account for the production of excess porphyrinuria. The most significant correlation in our studies was the evidence of hepatic dysfunction in almost all of our subjects who had porphyrinuria. The presence of liver dysfunction may explain the porphyrinuria of our pellagrins either in the form of a disturbance in hemoglobin breakdown and production of excessive coproporphyrin III, or of the liver's inability to excrete porphyrins into the bile.<sup>7</sup> Both mechanisms may be coincidentally involved. Dobriner, Strain, and Localio<sup>9b</sup> have reported the detailed analysis of the porphyrin excretion of a case of pellagra in an inebriate. They found a mixed type I and III coproporphyrin excretion similar to that reported in porphyria, pigment cirrhosis of the liver, and lead poisoning, and pointing to a pathologic construction as well as an abnormal excretion of porphyrin. These authors suggest that the porphyrinuria may resemble the urobilinuria caused by hepatic insufficiency.

As early as 1900 Garrod<sup>13</sup> had observed that many patients with porphyrinuria had evidence of liver disease, either clinically or post-mortem. More recently, Watson<sup>25a</sup> and Franke<sup>11</sup> have reported on the incidence of liver disease in porphyrinuria. Sydenstricker and his coworkers<sup>22,23</sup> and Boggs and Podget<sup>4</sup> have speculated on the possibility of some relationship of hepatic dysfunction to pellagra.

In our subjects we have had to consider one other factor, *i. e.*, the

chronic consumption of alcohol. Franke and Fikentscher<sup>12</sup> and Brugsch<sup>5</sup> attributed the porphyrinuria of inebriates to the presence of liver disease. The finding of porphyrinuria in a pellagrin may, therefore, in our opinion, be only a sign of sufficient hepatic damage to interfere with the normal handling of the porphyrins.

**Conclusions.** 1. Porphyrinuria is not a constant guide for the diagnosis of, or for the evaluation of therapy in, pellagra.

2. When present in pellagra, the porphyrinuria is probably a manifestation of the coincident existence of hepatic dysfunction.

We wish to express our gratitude to Dr. Konrad Dobriner for supplying us with the standard porphyrin solutions and for his helpful advice during the course of this work.

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## BOOK REVIEWS AND NOTICES

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CONGENITAL CLEFT LIP, CLEFT PALATE, AND ASSOCIATED NASAL DEFORMITIES. By HAROLD STEARNS VAUGHAN, M.D., D.D.S., F.A.C.S., Professor of Clinical Surgery, New York Post-Graduate Medical School, Columbia University; Attending Surgeon, New York Post-Graduate Hospital, etc. Pp. 210; 259 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

THIS is a concise presentation of the subject of cleft lip and palate. After an introduction on historic data, there follow chapters on embryology and anatomy of the parts concerned, and a description of the various types of deformity. There is a simple exposition of the physiology of speech and deglutition with an explanation of the mechanism of cleft palate speech. The author describes several of the well-known operative methods of treatment, giving details of those which have been found most efficacious in his hands. This is not a mere recital of operations, but is of real value as expressing the results of the author's wide personal experience in this field. For repair of cleft palate, he employs the von Langenbeck operation, using the lead ribbon support for the flaps as developed by Mackenty and himself. For the short palate, he uses his modification of the Dorrance "push-back" operation, which is designed to avoid an opening anteriorly when the cleft originally extends into the hard palate. The author deals at some length with the importance of continued supervision of the patient after operation. He states that young children with adequate velopharyngeal closure obtain normal speech, even without training, but notices that adequate speech training and exercises will produce the results more rapidly. He also stresses the importance of orthodontic treatment when indicated. There is a section by Dr. L. J. Porter describing useful orthodontic appliances in these cases, and one by Dr. J. J. Fitz-Gibbon upon prosthetic aids in cases with defects not amenable to operation.

We commend this book as one containing reliable information based upon wide personal experience in a very difficult field too often invaded by insufficiently prepared surgeons.

R. I.

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DIE KATARRH-INFEKTION ALS CHRONISCHE ALLGEMEINERKRANKUNG. Eine dynamische Reaktionspathologie des Rheumatismus und ätiologisch zugehöriger Erkrankungen als Ausdruck einer spezifischen Virusinfektion. By DR. MED. K. v. NEERGAARD, Professor an der Universität Zurich. Pp. 285; 24 illustrations. Leipzig: Theodor Steinkopff, 1939. Price, Paper, Rm. 11.25; Bound, Rm. 12.37.

THIS interesting book deals chiefly with the sequels of common cold and influenza. It is pointed out that there is no borderline between these two diseases, and that their sequels are the same. As they are toxic in nature, and as the infection by which they are preceded is most often a catarrhal one, they are spoken of as catarrhal toxicoses. The author describes in detail the various symptoms and manifestations of catarrhal toxicosis. He discusses its differential diagnosis, and its relationship to other diseases such as bronchitis, pneumonia, nephritis and especially rheumatism in its various forms. He also gives a comprehensive review of its etiology and pathogenesis. The author concludes that the common cold and influenza

are the cause of a "permanent endemic of chronic diseases of various nature and localization." This catarrhal toxicosis as well as the common cold and influenza should be regarded as part of one specific infectious disease that was caused by the influenza virus. W. E.

**FUNCTIONAL DISORDERS OF THE FOOT.** By FRANK D. DICKSON, M.D., F.A.C.S., Orthopedic Surgeon, St. Luke's, Kansas City General, and Wheatley Hospitals, Kansas City, Mo., Providence Hospital, Kansas City, Kansas, and REX L. DIVELEY, A.B., M.D., F.A.C.S., Orthopedic Surgeon, St. Luke's, Kansas City General, Research, and Wheatley Hospitals, Kansas City, Mo., Providence Hospital, Kansas City, Kansas. Pp. 305; 202 illustrations. Philadelphia: J. B. Lippincott Company, 1939. Price, \$5.00.

A SOUND and practical work, lacking in brilliance and originality, G. W.

**ORTHOPEDIC OPERATIONS. Indications, Technique and End Results.** By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City. Pp. 766; 865 illustrations on 322 figures. Springfield, Ill.: Charles C Thomas, 1940. Price, \$9.00.

THE essence and substance of this most excellent textbook are fully indicated in its title. A vast amount of material covering an extremely broad field is presented in a terse, at times, almost laconic style. The illustrations are numerous, clear and essential. The value of the work is greatly enhanced by its complete index.

Such a work could only be written by a surgeon who is master of his specialty. When to this is added the preëminent scholarship of the author, the result is a text outstanding in the world's literature upon this subject.

G. W.

**A DOCTOR'S HOLIDAY IN IRAN.** By ROSALIE SLAUGHTER MORTON, M.D., Author of "A Woman Surgeon." Foreword by Surgeon-General HUGH S. CUMMING (RETIRED). Pp. 335; illustrated. New York: Funk & Wagnall Company, 1940. Price, \$3.00.

THE author, well known for her medical achievements in the World War and as the author of an arresting autobiography, "A Woman Surgeon," has visited Iran (Persia) to observe at first hand the metamorphosis of a reborn country. More than merely recording a doctor's holiday, she describes enthusiastically the country's political and social progress under Reza Pahlavi, and almost incidentally considers the part played by the doctor in the country's advancement. Most of these 50 pages, too, depict the backward state of medical knowledge in Iran, the work of foreigners apparently constituting the chief redeeming feature thus far. However, the number of better educated Iranian physicians is increasing, public health measures being adopted by the government, free dispensaries opened and vaccination made compulsory for children. Here is entertaining and instructive reading in support of the author's belief that there is a great future for this ancient country that has had its periods of greatness.

E. K.

**AN INTRODUCTION TO MODERN GENETICS.** By C. H. WADDINGTON, Sc.D., Fellow of Christ's College, Cambridge. Pp. 441; 159 illustrations and 5 plates. New York: The Macmillan Company, 1939. Price, \$4.00.

HEREDITY, the subject matter of genetics, has to an increasing degree become of importance to medicine. While this is widely realized, few prac-

tioners are correspondingly well acquainted with the principles upon which the science of genetics is built. This work deals with the concepts and theories of genetics, rather than with techniques which have so often been over-emphasized in texts on the subject. The first part of the book treats of formal genetics, *i. e.*, the fundamentals of Mendelism, the mechanics of the chromosomes and related subjects; in the second part genetics and development are discussed; in the third part, genetics and evolution; in the fourth, genetics and human affairs; the fifth deals with the nature of the gene. Perhaps the fact that this book was written by a well-known experimental embryologist accounts for the lucidity and perspective with which the subject is treated. It will be well worth the reading of anyone who would gain a survey of this relatively new science. B. L.

**DIE AKUTE MYOKARDITIS.** Klinische und pathologisch-anatomische Beobachtungen bei 36 Krankheitsfällen in ihren Beziehungen zu Herd-Infekten, zu Allgemein-Infekten (Grippe) und zur Tuberkulose. By FERDINAND WUHRMANN, Oberarzt der Klinik. Pp. 148; 86 illustrations. Basel: S. Karger A.-G., 1939.

THIS is an interesting study of 36 cases of acute myocarditis other than diphtheric, scarlatinal, typhoid, septic or rheumatic. A large group of these cases was preceded by influenza; 15 cases were affected with exudative pulmonary tuberculosis; and a few had a focal infection. The myocarditis commenced as a rule suddenly with collapse, cyanosis, rapid pulse and dyspnea. The heart was either a little enlarged or dilated, and electrocardiographic changes were present. In most cases death ensued rapidly, though occasionally recovery occurred. Histologic examination showed edema and inflammatory infiltration, both lymphocytic and granulocytic. The infiltrations were but rarely diffuse, but mostly focal, either in the auricles or the ventricles or both. The endocardium and pericardium were not affected. The author believes that post-influenzal myocarditis should be explained on an allergic basis, while tuberculous myocarditis is a "true tuberculous interstitial myocarditis." The last chapter offers a critical discussion of the literature of the last 50 years. The monograph is well illustrated by many Roentgen rays, electrocardiograms, charts and microphotographs.

W. E.

**DIE FUNKTION DER NEBENNIERENRINDE.** By F. VERZÁR, Professor der Physiologie an der Universität Basel. Pp. 266; 16 illustrations and 4 tables. Basel: Benno Schwabe & Co., 1939. Price, Fr.Sw.25.00.

THE author has succeeded in presenting a well organized summary of adrenal physiology. Emphasis is placed upon experiments dealing with phosphorylation; and, in addition, a theory of adrenal function is suggested. This is a valuable reference book. C. D.

**MANUAL OF THE DISEASES OF THE EYE.** For Students and General Practitioners. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York, etc. With the assistance of CHARLES A. PERERA, M.D., Instructor in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia University, New York. Pp. 515; 387 illustrations including 31 plates with 95 colored figures. Sixteenth Edition, revised. Baltimore: William Wood & Co., 1939. Price, \$4.00.

THIS sixteenth edition has been carefully revised so that although new material has been added the size of the volume stays approximately the same.



Some of the recent additions concern chemotherapy, the operative treatment of retinal detachment by electrocoagulation and of corneal opacities by keratoplasty. The colored illustrations are sharp and accurate. This manual forms a reliable basis for the introduction of the undergraduate student to ophthalmology and an accurate reference manual for the general practitioner.

W. F.

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**VIRUS AND RICKETTSIAL DISEASES** with Especial Consideration of Their Public Health Significance. A Symposium held at The Harvard School of Public Health June 12-17, 1939. Pp. 907; illustrated. Cambridge, Mass.: Harvard University Press, 1940. Price, \$6.50.

DISEASES caused by viruses are now known to be as numerous and as important as are the bacterial infections. But the study of viruses is still in an early stage, and progress in our knowledge is rapid; hence this survey by a group of qualified investigators is timely and very helpful. The book deals with major problems: the nature and properties of viruses, the common diseases of man and animals caused by them, the epidemiological aspects of virus diseases, the peculiar relationship of some bacterial infections and virus infections, insects as vectors of viruses. These and related topics discussed are of every day importance to the practitioner and to the public health official to whom this book is warmly recommended. A comprehensive index would render this useful and stimulating work even more helpful.

B. L.

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**EPIDEMIC ENCEPHALITIS. ETIOLOGY, EPIDEMIOLOGY, TREATMENT.** Third Report by the Matheson Commission, WILLARD C. RAPPLEYE, Chairman, HAVEN EMERSON, ALPHONSE R. DOCHEZ, FREDERICK P. GAY, WILLIAM H. PARK, CHARLES R. STOCKARD, FREDERICK TILNEY, WILLIS D. WOOD. HUBERT S. HOWE, Secretary, JOSEPHINE B. NEAL, Executive Secretary, HELEN HARRINGTON, Epidemiologist. Pp. 493. New York: Columbia University Press, 1939. Price, \$3.00.

THE discovery during the past decade of the causative agents of several specific types of encephalitis has aroused wide-spread interest in these infections of the brain. This report comes therefore as a timely and welcome summary of recent work on this subject.

The major part of this book is a bibliography of the literature of encephalitis for the years 1930 to 1937, which runs to some 300 pages. The chief contributions of this literature are necessarily reviewed but briefly, as they include the epidemic encephalitis of von Economo, the St. Louis and Japanese types, equine encephalo-myelitis, post-infectious encephalitis and other allied ills.

In addition to this bibliographic work the Commission reports on their attempts to isolate infectious agents from encephalitic cases. Over 150 specimens of spinal fluid and of blood taken during the "ante" stage of the disease were injected into mice and rabbits with completely negative results. On the other hand, by inoculation of brain tissue from patients dying of various forms of encephalitis, a virus was found in five of 50 cases. In three instances of measles encephalitis, and in a chronic encephalitis case a herpes virus was recovered. Although no claim is made that herpes virus is the cause of epidemic encephalitis, the Commission was led by these results to a trial of virus vaccine treatment.

Virus vaccine made up from herpes virus has been used since 1933 in 88 cases in the acute stage with a mortality rate of less than half that of the untreated cases. Patients in the chronic stage have also been treated with results "on the whole encouraging and at times quite spectacular." The authors wisely point out the difficulty in evaluating these results.

This volume is a splendid reference source for the literature of encephalitis. For the general reader its value could have been increased if the review had been more critical even if less encyclopedic, and had the titles been listed under subjects rather than authors. G. G.

**HUMAN HELMINTHOLOGY.** A Manual for Physicians, Sanitarians and Medical Zoölogists. By ERNEST CARROLL FAUST, A.B., M.A., PH.D., Professor of Parasitology and Director of Laboratories, Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 780; 302 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, \$8.50.

In its second edition this book has been increased by more than 150 pages part of which is taken up by a new chapter "Anthelmintics and Their Use" and part by increases in other portions of the text. The classification of the Nematelminthes has been revised, but probably would have been improved by more complete illustrations. Although it is still possible to point to many other faults, these are chiefly of a minor nature and the book seems to be the most complete and useful in its field. H. R.

### NEW BOOKS

*Arthritis and Allied Conditions.* By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Ward Physician, Hospital of the University of Pennsylvania. Pp. 752; 200 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$8.50.

*Synopsis of Obstetrics.* By JENNINGS C. LITZENBERG, M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis. Pp. 394; 157 illustrations (5 in color). St. Louis: The C. V. Mosby Company, 1940. Price, \$4.50.

*Handbook of the Hospital Corps, United States Navy, 1939.* Pp. 1015; 201 illustrations. Washington, D. C.: The Bureau of Medicine and Surgery, under the Authority of The Secretary of the Navy, 1939. Price, \$1.75 (Buckram).

Though written as a guide for the hospital corpsmen of the Navy, this book contains such a mass of information that it should be useful in much wider circles. Minor surgery, anesthesia, therapeutics, toxicology, pharmacy, nursing, allergy, venereal disease, industrial medicine, are but a few of the subjects covered in the 12 chapters. The most detailed treatment is naturally expended on the 12 sections of the final chapter on Hospital Corps Technical Specialties.

*Chemotherapy and Serum Therapy of Pneumonia.* By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School; Member of the Board of Consultation, Massachusetts General Hospital, ELLIOTT S. ROBINSON, M.D., PH.D., Director, Division of Biologic Laboratories, Massachusetts Department of Public Health, and RODERICK HEFFRON, M.D., Medical Associate, The Commonwealth Fund; formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 174. New York: The Commonwealth Fund, 1940. Price, \$1.00.

*Introduction to Medicine.* By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician, Medical Division of the Cook County Hospital, etc. With Introduction by ADA BELLE McCLEERY, R.N., Superintendent, Evanston Hospital, Evanston, Illinois. Pp. 642; 144 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.25.

*Graduate Medical Education in the United States.* Continuation Study for Practicing Physicians, 1937 to 1940. Pp. 243. Chicago: American Medical Association, 1940.

*Poisons, Their Isolation and Identification.* By FRANK BAMFORD, B.Sc., Late Director of the Medico-Legal Laboratory, Cairo. With a Foreword by PROFESSOR SYDNEY SMITH, M.D., F.R.C.P., Regius Professor of Forensic Medicine, University of Edinburgh. Pp. 344; 21 illustrations. Philadelphia: The Blakiston Company, 1940. Price, \$4.00.

*The British Encyclopædia of Medical Practice* including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Cumulative Supplement, 1939* (Pp. 170; 1 illustration); *Surveys and Abstracts, 1939* (Pp. 655; 26 illustrations). Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. Publishing Editor, ADAM CLARK, L.M.S.S.A.; Sub-Editor, G. FAULKNER, D.Sc. London: Butterworth & Co. (Publishers), Ltd., 1940. Price, \$9.00 per volume.

*Specialties in Medical Practice.* Volumes 1 and 2. Edited by EDGAR VAN NUYS ALLEN, M.D., Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester; Associate Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. With a Foreword by DONALD C. BALFOUR, M.D., F.A.C.S., F.R.C.S. (England), F.R.A.C.S., Consultant in Surgery, The Mayo Clinic; Professor of Surgery and Director, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 964; 300 illustrations. New York: Thomas Nelson & Sons, 1940. Price, \$25.00.

*Relation of Trauma to New Growths. Medico-Legal Aspects.* By R. J. BEHAN, M.D., DR. MED. (Berlin), F.A.C.S., Surgeon, St. Joseph's Hospital and Dispensary, City of Pittsburgh Hospital at Mayview, The Tuberculosis Hospital at Leech Farm, and the Allegheny County Hospital at Woodville. Pp. 425. Baltimore: The Williams & Wilkins Company, 1939. Price, \$5.00.

*The Hypothalamus and Central Levels of Autonomic Function.* Proceedings of the Association December 20 and 21, 1939, New York. (Vol. XX of Research Publications, Association for Research in Nervous and Mental Diseases.) Pp. 980; 319 illustrations and 35 tables. Baltimore: The Williams & Wilkins Company, 1940. Price, \$10.00.

### NEW EDITIONS

*A Textbook of Physiology.* By WILLIAM D. ZOETHOUT, Ph.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University) and W. W. TUTTLE, Ph.D., Professor of Physiology, College of Medicine, State University of Iowa. Pp. 743; 302 illustrations. Seventh Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$4.50.

This book maintains its high standard of clearness of exposition. Treating the subject for students with relatively little scientific background, it deals with chemical and histologic foundations in a simple but adequate manner. It gives special attention to applications and rightly emphasizes the practical dietetics and the value of vitamins. It contains many references to review articles including recent publications and should be a very useful guide for students. It has been brought up to date with good judgment. H. B.

*Diabetes. Practical Suggestions for Doctor and Patient.* By EDWARD L. BORZT, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Chief of Medical Service B, The Lankenau Hospital, Philadelphia. With a Foreword by GEORGE MORRIS PIERSON, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Pp. 296; 15 illustrations and 6 tables. Second Edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1940. Price, \$2.50.

# PROGRESS OF MEDICAL SCIENCE

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## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## SINUSITIS IN CHILDREN

LATELY sinus disease in children, a process inadequately studied and for some unknown reason neglected by rhinologists, pediatricians and general practitioners, has begun to attract widespread attention<sup>6,12</sup> and thoughtful consideration. Since children are especially subject to recurring attacks of upper respiratory infection, sinusitis should be suspected in cases with continued nasal obstruction, chronic cough, or frequent "colds." Persistent purulent nasal discharge may imply something more than a "cold," so that Miller<sup>7</sup> regards every acute "cold" as potentially an acute sinusitis, and Wachsberger<sup>13</sup> believes that most of the chronic sinus infections of adults can be traced back to early childhood. Sinusitis may be a complication of the acute exanthematous diseases, particularly scarlet fever and measles, as well as of whooping cough, influenza and any acute respiratory tract infection. Predisposing factors for the establishment of sinusitis are undernourishment, poor hygienic surroundings, inadequate diet, constitutional defects, and anything that causes mechanical obstruction to normal aëration and ventilation.

Mitchell<sup>8b</sup> declares that the time to prevent infantile sinuses and accompanying sinusitis is during the period of growth and development, that is, during childhood and early adolescence. When the tonsils are removed too early in life, additional work is thrown on the sinuses, which play an intimate part in immunization against diseases that may arise from infections of the upper part of the respiratory tract. The dictum "once a sinus always a sinus" is not true if the condition is recognized early and managed properly. Mitchell<sup>8a</sup> states that the radiologist should be consulted at regular intervals so that the progress

of the disease may be determined. The otolaryngologist assumes responsibility for local treatment, while the pediatrician must recognize the sinus disease and supervise the general health of the patient. According to Birdsall<sup>3</sup> the onset of sinusitis is often insidious and may be overlooked unless a careful nasal examination is made. Tonsillectomy, performed upon children with sinusitis, is frequently without beneficial effect. Careful examination of the nose would prevent this error in judgment in a large percentage of cases. Sinusitis in children responds readily to conservative treatment; operative intervention is necessary only in a relatively small number of cases.

In order to arrive at an accurate diagnosis and to obtain better results in the treatment of nasal disease in children, Barnett and Carnahan<sup>2</sup> stress the desirability for establishing an allergy-conscious attitude on the parts of the rhinologist and the pediatrician. To determine the extent of nasal allergy in childhood it is essential to perform routine examinations of the nasal secretions. In a child with uncontrolled allergy the removal of infected tonsils and adenoids may aggravate symptoms. The results from surgical intervention are often disappointing if associated allergy is not simultaneously or previously relieved. The removal of nasal polyps in the patient with uncontrolled allergy may be followed by prompt recurrence. Cytologic examinations of the nasal secretions with predominance of eosinophils offer confirmatory evidence of allergy. Relief from nasal allergy may often be obtained by prophylactic allergic measures. Allergic testing and hyposensitization should be utilized in unrelieved and complicated conditions.

Acute osteomyelitis of the superior maxilla in children and in young infants is the subject of two excellent papers by Lacy and Engel<sup>5</sup> and by Asherson.<sup>1</sup> Acute osteomyelitis of the superior maxilla in infants presents a typical and constant clinical picture enabling the condition to be readily identified in spite of the rarity of its occurrence. Starting with a feverish attack, the onset is sudden. The first indication of the location of the disease is edema and swelling of the eyelid. The eyes become closed, and proptosis follows. There soon develops a unilateral purulent nasal discharge from which the staphylococcus can be cultured. The cheek on the affected side becomes red, swollen, painful and tender. The inflammation goes on to suppuration and usually ruptures just below the inner canthus, and gives rise to a persistent fistula. Localization may occur also in the region of the canine fossa, the alveolus and the palate with subsequent fistula formation. Early spontaneous rupture or operative procedures establish drainage of the infected bone and result in discharging fistulas. The outcome may be complete healing, healing with persistent sinus formation or the development of septicemia and subsequent death. Immediate operation is indicated when the child presents itself with an orbital, canine or alveolar abscess already formed. Drainage should be established through the mouth and through the maxillary antrum. During the chronic or indolent stage, further operation may be necessary to search for and remove any sequestra.

In outlining otolaryngologic suggestions in pediatric practice, Dintenfuss<sup>4</sup> maintains that pediatricians should remember that the prime object is to assist Nature in the treatment of acute sinusitis and acute rhinitis. The local treatment of the nose should be mild and irritating.

He asserts that the less intranasal treatment the better. Ephedrine and other shrinking solutions, while they produce temporary relief from nasal stuffiness, have the great disadvantage of causing secondary relaxation of the vascular layer of the submucous tissue, with resultant bogginess of the turbinates, interference with the normal flow of mucus and disturbance of ciliary movement. Miller<sup>7</sup> finds that the frequent use of inert liquid petrolatum in young children is contraindicated because of the danger of inducing lipoid pneumonia. Any surgical procedure should be undertaken in acute sinusitis only in the presence of some grave complication. The prognosis of chronic sinusitis in children is better than in adults when appropriate treatment is instituted.

Parkinson<sup>9</sup> utilizes the lateral head-low posture for making the nasosinusal area available for treatment, and ephedrine in a physiologic vehicle in the treatment of the nose and sinuses of children. In the posture described by Parkinson the head is inverted laterally. The patient lies on his side with his head bent downward exactly sidewise, using the shoulder as a fulcrum. Head-low posture in the treatment of the nose and sinuses makes available all important structures in the nose and permits treatment that is entirely free from trauma. Shea<sup>11</sup> insists that if the sinuses enter into the auto-immunization, a child possessing a normal group of sinuses obtains no help from cold serums, but a child with diseased or persistent infantile sinuses may need the help of a good vaccine. A modified autogenous vaccine made from the child's secretions obtained during the first cold of the winter may be employed. The vaccine is administered throughout the severe weather, one or two doses being given to maintain immunity. Intrasinus vaccine seems to hasten the coagulation of the discharge and clinically may have some merit.

Small doses of Roentgen rays, Rathbone<sup>10</sup> finds, appear to be a simple, safe and highly satisfactory method of therapy in chronic sinusitis in children. Over 700 children have been treated by him in this manner. Sinus disease in children is often masked by such complications as cough, pneumonia, otitis media and asthma. Those cases reported as cured improved immediately after treatment and have been symptom-free 1 to 4 years since treatment, and the check-up Roentgen examinations showed normal sinuses. Cases reported as improved were those in which the local symptoms and sequelæ were greatly or entirely relieved, but the check-up Roentgen examinations showed some degree of sinus disease still present. Cases reported as not improved had little or temporary improvement in symptoms, and the Roentgen examinations revealed sinus lesions.

NOAH D. FABRICANT, M.D.

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## NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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## EPILEPSY—PHYSIOLOGY AND THERAPY.

ALTHOUGH it may not be apparent in the physician's everyday activities, statistics show that epilepsy from the point of view of a disease entity surpasses any other single nervous and mental disorder in the number of its victims.<sup>14</sup> Novick<sup>42</sup> states that in the United States alone there are one and a half million persons subject to this illness. Lennox<sup>28a</sup> is of the opinion that there are approximately a half million persons in the United States who are or have been subject to seizures. This number approximates the incidence of diabetes or active tuberculosis. Forty thousand epileptic individuals are now confined in our state institutions, one-fourth in colonics designed especially for their care. The annual cost of care for these 40,000 individuals is approximately eighteen million dollars.

Of recent years very notable advances have been made in our understanding of the pathophysiology of convulsive disorders and new pharmacologic agents have been developed. In this review an attempt will be made to present the outstanding features of these developments, which are of such import that every physician should be acquainted with them.

It should be emphasized that epilepsy today is not regarded as a disease entity. Cobb<sup>4</sup> states, "It is a symptom of many cerebral diseases." He defines the condition as: "A disorder of the brain that causes repeated fits in which the usual functional abnormalities are: (1) changes in the electrical potentials as seen in the electro-encephalogram; (2) partial or complete loss of consciousness; (3) nervous discharge into smooth muscle, striated muscle or glands, causing involuntary visceral or motor behavior." Lennox<sup>28b</sup> is far more inclusive in his definition, including those who possess a characteristic "disturbance in the electrochemical activity of the discharging cells of the brain."

In approaching any case of convulsive disorder the primary concern of the physician should be to determine if possible the factor or factors causing the disturbance. Routine complete physical, neurologic, psychiatric, physiologic, and laboratory examinations should be conducted, and in the event these disclose nothing, encephalography should be performed. Brain tumors, meningeal scars, endocrine disorders, emotional disturbances, toxic conditions, inadequate physique, and poor regimen must be treated individually. Lennox<sup>28b</sup> states, "The most dramatic relief from seizures that I have seen was obtained by patients

who never took medicine for them." The cases in which no "symptomatic" factors are found remain as a residuum denoted as "essential" or idiopathic epilepsy.

A great number of physiologic investigations into essential epilepsy have been made of recent years. These have been well reviewed by Goldstein and McFarland.<sup>10</sup> Many alterations in blood sugar, electrolytes, carbon dioxide, and oxygen have been found to be physiologic after-products of convulsions rather than truly characteristic of the physiology of the epileptic individual. No clear-cut biochemical results, with the exception of a greater variability than that found in the normal, have been reported in epilepsy.

Gilks, Lennon, and Gilks<sup>11</sup> have recently shown that the carbon dioxide content of individuals with petit mal is high on the days when the fewest seizures occur and low on the days when many seizures occur, and that grand mal occurs in afflicted individuals when the carbon dioxide of arterial blood is at its height. Extreme fluctuation in carbon dioxide values rather than constant abnormality is the rule in patients with either of these conditions.

The most significant advances in the understanding of the physiology of convulsive disorders have come through the intensive work done in electro-encephalography. The background of this development was reviewed by Newman in these columns in 1933.<sup>12</sup> This apparatus records potential changes arising from the brain, these normally varying from 5 to 100 millionths of a volt and consisting in Alpha or "Berger rhythm" waves of 8 to 12 per second and Beta waves from about 18 to 30 per second, as illustrated in Chart I.

The electro-encephalographic tracing for each individual is quite permanently characteristic for him. We owe Gilks and Lennon<sup>13</sup> for the bulk of present information regarding electro-encephalography in epilepsy and their families. They have shown that each type of seizure is accompanied by a characteristic disturbance in the normal electric activity of the brain. The few seizures not accompanied by abnormal cortical rhythms were bizarre in their patterns. So positive are the findings that they permit of positive differential diagnosis between hysteria (which shows no abnormality in electro-encephalogram) and typical grand mal. The characteristic dysrhythmia for grand mal discloses waves appearing as sharp spikes with a frequency up to 25 or 30 per second. In psychomotor attacks the rate drops to 3 or 4 a second with square flat top waves predominating, while in petit mal quick sharp spikes and slow round waves at a rate of 3 per second alternate. The three typical forms of electro-encephalographic disturbance are found regardless of whether the seizure is caused by brain tumor, cortical birth injury, disturbance of blood sugar, or calcium level, or constitutional instability of rhythm control mechanisms.<sup>14</sup>

Although the abnormal rhythms are considered the cause of the seizures the fundamental disorder is not the abnormal rhythm but rather a defective control of rhythm. The sleep center presumably helps to regulate cerebral rhythms. Physical chemical changes in the body are likewise important. In the epilepsies the stability of rhythm control is poor so that any condition such as excitement, closing the



eyes, falling asleep, waking, or emotional upsets, which tend to produce rather sudden changes in normal rhythm are apt to precipitate seizures in these afflicted individuals.

Not only do characteristic electro-encephalographic changes occur concomitant with seizures but they often occur extrinsic of any clinical evidences of an attack. These subclinical attacks are more frequent in petit mal than in grand mal. The former condition is sometimes found in individuals not suspected of having it and may even occur during sleep.<sup>31</sup> Characteristic electrical crises of dysrhythmia appear in approximately 6% of normal control individuals and in 54% of relatives of epileptic individuals. Lowenbach,<sup>33</sup> and Strauss, Rahm, and Barrera<sup>52</sup> have continued electro-encephalographic researches on the relatives of epileptics and reported similar observations. Subclinical tracings may be of the same pattern found during clinical seizure, diminished in duration and voltage, or reveal themselves through isolated abnormal waves of large voltage, having the form of single sharp spikes, a spike and rounded hump, or square or round topped slow waves.

#### SAMPLE PATTERNS OF BRAIN WAVES IN VARIOUS CONDITIONS

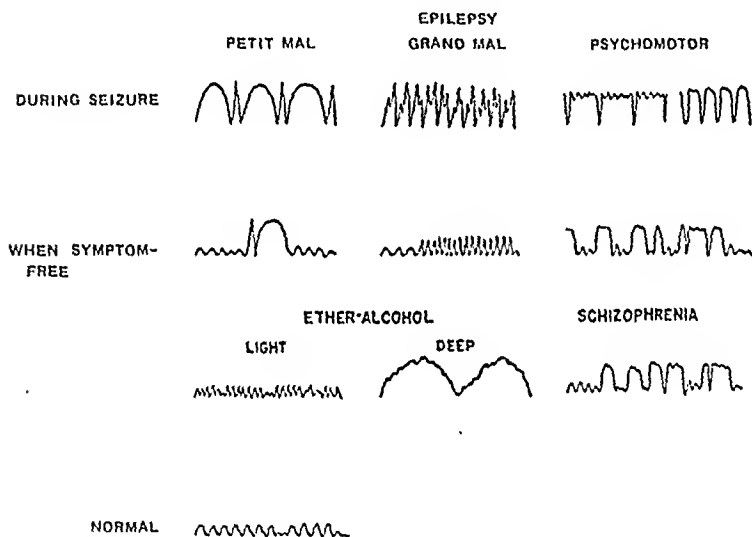


CHART 1.—Schematic patterns of brain waves encountered in various conditions. Not only the frequency of waves, but the relationship between slow and fast waves is significant. The uppermost row of curves indicates the pattern of brain waves during various types of epileptic seizures. The second row indicates the pattern in these same patients at times when they are free of seizures. The third row shows the pattern in patients under the influence of ether and of alcohol and a patient with schizophrenia. At the bottom is a portion of a normal curve for purposes of comparison. (Through the courtesy of Lennox, the tracings in Chart 1 are presented.)

Experienced electroencephalographers can now predict the occurrence of a seizure through careful study of the wave changes in a patient's record. Abnormal rhythms commonly appear first in the frontal area but frequently they appear first in the parietal or occipital areas.

The effects of various therapies on the electro-encephalogram have been studied, phenobarbital and bromide bringing about a decrease in the rate of cerebral rhythm, it being of value therefore in conditions of

abnormally fast rate, namely grand mal. Overdoses may decelerate cerebral discharges to the point of precipitating psychomotor episodes.<sup>32</sup> Petit mal rhythms may be precipitated by short periods of over-ventilation and often disappear while the patient is breathing air containing 3 to 7% carbon dioxide. Abnormal rhythms are greatly increased by insulin and decreased by glucose. Normal mental activity tends to inhibit and unpleasant emotional states to augment the frequency of petit mal rhythms.

The evidence of hereditary transmission of "paroxysmal cerebral dysrhythmia" is based not only on the findings in the electro-encephalograms of the relatives of epileptics<sup>31</sup> but is fortified by the fact that the individual who develops seizures after injury has 3 times more near relatives with seizures than the non-epileptic.<sup>29</sup> Lennox, Gibbs and Gibbs<sup>31</sup> found that of the 50% of the relatives of epileptic patients showing cortical dysrhythmia, 2½% have or have had epilepsy, indicating that those with a pre-disposition outnumber the clinical cases by 20 to 1. They reason that since 0.5% of the population is epileptic, 10% of the population is predisposed to epilepsy or a kindred disorder. The chance possibility of two pre-disposed persons marrying is one in a hundred, yet pre-disposition was found in both parents in 28% of their cases. It is therefore unwise for an epileptic person or one with a cortical dysrhythmia to marry a person who does not have normal brain waves.

Diagnostic problems in epilepsy have been somewhat clarified with the advent of electro-encephalography. It must be emphasized that this is a highly technical procedure requiring expensive apparatus and trained personnel. The diagnostic procedure of giving the patient large amounts of water (300 to 500 cc. of water every 1 to 2 hours) combined with pitressin (.25 to .5 cc. every 4 hours for 10 injections) as proposed by McQuarrie<sup>35-37</sup> and others has proved itself to be fairly reliable.<sup>65</sup> The advantage of this test is that it can be administered in practically any hospital and is safe if properly conducted.

Nachtsheim<sup>41</sup> has reported that far smaller doses of metrazol are required to produce a generalized convulsion in epileptic animals than in non-epileptic animals and has proposed that this fact might be of diagnostic value in suspected epilepsy. Further studies may be necessary to determine the exact dosage limits which would permit a positive diagnostic statement. Experience with a few epileptics who have had metrazol treatment for other disorders gives the impression that these individuals require much smaller convulsive doses of the drug than do non-epileptic persons.

The concept that practically all persons with epilepsy deteriorate has been challenged by Paskind and Brown<sup>46a</sup> who found that in a group of 304 epileptic persons, all of whom had had the disease at least 6 years, only 6.5% showed any deterioration. The statement that most textbook and standardized opinions concerning epilepsy have been based upon advanced committed cases and have not taken into account mild or uncommitted cases is pertinent. These authors conclude that constitutional differences reflected in both size and proportions are present in deteriorated epileptic patients as compared with non-deteriorated ones. Clark<sup>3</sup> and Bleuler<sup>2</sup> have observed that abnormalities

prognosticating epileptic personality and deterioration are present in patients before the onset of any seizures. The non-deteriorated epileptic in general has fewer seizures, more and longer remissions, and the onset of his illness is later in life than in the institutional patient.<sup>30,45b,c</sup> Jasper and Nicols<sup>23</sup> and Hyland, Goodwin, and Hall<sup>21</sup> have emphasized the possibility that reported subclinical seizures evidenced by electroencephalographic tracings may be an important factor in the mental retardation and emotional disturbance seen in epileptic patients between or without attacks.

Since ancient times, epileptics have been plied with practically every type of substance and therapeutic agent known to man, including powdered human skull, gall of boar, fried with urine, elks' claws, liver of wolf, and so on.<sup>54</sup> Effective therapy in the last 100 years has consisted primarily in the dependence upon bromides and phenobarbital. Cohen, Showstack, and Myerson<sup>7</sup> have divided the history of pharmacologic treatment of epilepsy into 3 epochs, the first beginning in 1853 with the increasing use of bromides, the second in 1912 with the introduction of phenobarbital, and the third in 1938 when dilantin sodium was made available by Merritt and Putnam.<sup>40a</sup> For 50 years after their introduction bromides held undisputed first place in the treatment of seizures. In 1899 the National Hospital in Queen's Square, London, dispensed almost 2 tons of this medication.<sup>16</sup>

Although bromides have been abandoned by most clinicians because of the possible toxic effects, including clouding of consciousness, delirium, and skin manifestations, some experienced clinicians continue to use them to advantage. Pollock<sup>46</sup> reports that in 96 cases he secured final remissions in 36% and remissions of over 1 year in 71.7% of his cases, some of these lasting as long as 10 years with a mean of between 3 and 4 years. Excluding focal attacks he was able to stop seizures in 74% of his cases by using bromides.

Novick<sup>42</sup> recommends that large doses of bromide be administered these patients and states, "Bromide is probably the most effective anti-convulsant." He has found the drug useful in those cases not responding to phenobarbital. Although phenobarbital was synthesized<sup>10</sup> in 1903 it was not used in epilepsy until 1912<sup>19</sup> and its use in this country was first reported in 1920 by Grinker.<sup>17</sup> Since that time this drug has come to be almost universally used in the treatment of all forms of epilepsy. Individual dosage is very important in securing satisfactory relief. The drug has not been very effective in petit mal. Some individuals have shown idiosyncrasy to it and in others adequate dosage has been impossible because of the stupor and clouding of consciousness which were produced.

Southerland<sup>51</sup> has recently reported that in a group of institutional cases 85% had fewer seizures on phenobarbital, gr. I per morning, and sodium bromide, gr. XXX per afternoon, than when receiving phenobarbital, gr. I, twice daily. Somerfeld-Ziskind and Ziskind<sup>50</sup> report that by using phenobarbital alone they have completely relieved 79% of 48 patients from attacks. Robinson and Osgood<sup>49</sup> report that 37 of 100 patients derived "marked benefit" from large doses of phenobarbital. The average daily dose was  $3\frac{1}{4}$  grains and the maximum  $11\frac{1}{4}$  grains. Cohen, Showstack, and Myerson<sup>7</sup> determined that the maximum

effective dose of phenobarbital was able to bring about improvement in 89% of 144 patients and a total seizure reduction of 68%. Cohen and Myerson<sup>6</sup> have been able to eliminate some of the undesirable sedative effects of phenobarbital by giving 5 to 25 mg. daily of amphetamine sulphate without in any way diminishing the anti-convulsant effect of phenobarbital. This demonstrates the fact that phenobarbital is not dependent upon its sedative action for its clinical value in epilepsy.

The ketogenic diet has been used for some years in the treatment of epilepsy, but due to the difficulties incident to having patients remain strictly on it, it has never been widely utilized. Helmholz<sup>20</sup> after 15 years' experience with ketogenic diet in 404 epileptic children reports that 31% were rendered free of attacks and 16% definitely improved. Wilson<sup>55</sup> reports that the regimen has repeatedly failed to help in the therapy of extramural patients.

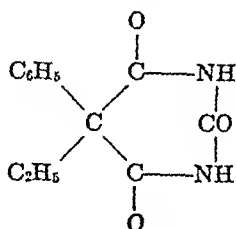
Fluid restriction and dehydration regimen as recommended by Fay<sup>9</sup> did not yield good results in the Wilson clinic because of difficulty in securing coöperation in patients. This procedure has been quite generally adopted but usually in conjunction with drug therapy.

Of recent years there has been used in England a barbituric acid derivative called prominal, namely N-methyl-ethyl-phenyl-malonylurea. A claim has been made that this drug has none of the unfortunate side actions of phenobarbital. Page<sup>44</sup> reports having reduced the total number of seizures in 10 of his patients by more than 50%. Millman<sup>40</sup> after 5 years' experience with the drug in an epileptic colony concludes that it is superior to phenobarbital in the majority of cases, that it is less hypnotic, does not diminish in efficacy over a period of 5 years.

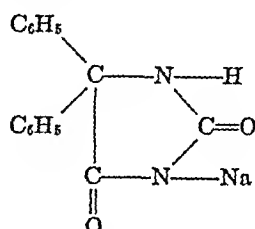
Methylene blue has been used by Kajdi and Taylor<sup>24</sup> in status epilepticus while neutral red and brilliant vital red have been used by Cobb, Cohen, and Ney<sup>5</sup> with encouraging results. Osgood and Robinson<sup>43</sup> report that brilliant vital red diminished the attacks in over one-half of 13 cases treated and had a greater anti-convulsant effect on petit mal than grand mal seizures. These dyes will probably have no widespread therapeutic acceptance or possibilities because of the manner in which they discolor the subject.

The most remarkable and important chemotherapeutic agent to appear in the convulsive disorders since 1912 was developed under interesting circumstances in Boston by Putnam and Merritt in 1937.<sup>48</sup> They reported upon a reliable electrical method for producing convulsions in cats and were able to establish convulsive thresholds within quite exact limits without notable injury to test animals. With the aid of this apparatus they proceeded to test the anti-convulsant activity of a rather large number of drugs and found, for instance, that sufficient sodium bromide to prevent a cat from walking would raise the convulsive threshold about 50% while a similar dose of phenobarbital would treble or quadruple it. The most promising drugs found were diphenylhydantoin, acetophenone, and benzophenone. An interesting observation was that barbiturates other than phenobarbital had very little anti-convulsant action. Dilantin and phenobarbital raised the convulsive threshold greatly at first but with continued administration the threshold fell to normal limits.<sup>34</sup> The drugs found most effective were those possessing the largest number of phenyl radicals. The structural

formulae of sodium diphenylhydantoinate and phenobarbital are shown to aid in the understanding of the clinical relationship of these drugs.



Phenylethylbarbituric acid



Sodium diphenylhydantoinate.

Further observations along these same lines were reported in 1938. At this time a number of convulsive drugs were also tested.<sup>39</sup> Sodium diphenylhydantoinate was then subjected to extensive pharmacologic and toxicologic tests by Krayer<sup>27</sup> and Kamm and Gruhzt.<sup>25</sup> The results were such that the drug was considered safe for clinical trial. Later in 1938 first clinical results were reported upon 142 patients treated for periods of 2 to 11 months.<sup>40b</sup> Grand mal attacks were relieved in 58%, greatly decreased in frequency in 27%. Petit mal were relieved in 35% and greatly decreased in frequency in 49%. Psychic equivalents were relieved in 67% and greatly reduced in 33%. Toxic manifestations were reported in 15%.

The widespread usage and acceptance of this agent has been based largely on the facts that it has no sedative effect, no serious toxic effects, and is a most effective anti-convulsant. Frost<sup>41</sup> on a basis of 3 cases, 1 schizophrenic and 2 epileptics, has reported that the threshold to metrazol was not raised after administering dilantin. Goldstein and Weinberg,<sup>45</sup> however, report that in 19 epileptic patients given dilantin for 1 month or longer and then given metrazol the convulsive threshold was so raised that whereas before dilantin 52% of the individuals responded with seizures, only 7% responded after dilantin.

Individuals who have been receiving other forms of medication and are being placed upon dilantin should not be suddenly taken off the one and given the other but the previous drug should slowly be withdrawn over a period of about a week during which the dilantin dosage is being built up. Dilantin at the present time is available in 1½ grain capsules and ½ grain capsules and is best taken with or after meals because in some individuals the basic nature of the salt produces nausea when taken on an empty stomach. The usual procedure is to start adults with .3 gm. daily of dilantin (3 capsules) and after previous medication has been withdrawn to continue on this dosage until sufficient time has elapsed to determine its effectiveness. If it proves ineffective, then the dosage is slowly increased to as much as .6 gm. daily.

Sodium diphenylhydantoinate was approved by the Council on Pharmacy and Chemistry<sup>1</sup> in November, 1939, at which time the reports of 13 clinicians were presented, covering a total of 595 epileptic patients. In 404 of these patients the clinicians reported that this drug was the most effective of a number submitted. The drug was approved under the name Dilantin Sodium and accepted for inclusion in the New and Non-official Remedies with the provision that it not be recommended

for use by the general practitioner unless he is able to maintain close daily supervision of the patient and it is not to be recommended for treatment of those patients whose seizures occur only at long intervals unless phenobarbital is not effective or induces disagreeable side actions.

Kimball and Horan<sup>26</sup> reported that in 55 % of their 220 cases seizures were entirely controlled. They were modified or partially controlled in another 20 % and there was no improvement in 25 %. McCartan and Carson<sup>34</sup> were able to secure a complete cessation of grand mal convulsions in 79 % of cases treated by them and a marked decrease in 10.5 %. Weinberg and Goldstein<sup>53</sup> report that in a series of 15 patients treated first with phenobarbital and then with dilantin the latter drug produced complete cessation of seizures in 40 % and a marked diminution in 13 % of the cases. Numerous other reports have appeared in the literature, in general agreeing with the findings given above, the two major advantages of this drug being its greater effectiveness in controlling grand mal and psychomotor seizures and its absence of hypnotic effect. The drug has had but small therapeutic value in petit mal.

Several authors have been using combinations of dilantin and phenobarbital in cases not responding satisfactorily to either with much better results than could be secured with either drug separately. Cohen, Showstack, and Myerson<sup>7</sup> found that dilantin alone did not exert as favorable an effect as adequate phenobarbital alone but disclosed a most striking synergism between phenobarbital and dilantin in combination, the reduction in seizure incidence being at least 50 % above the most favorable results obtained by either drug alone. They recommend the use of amphetamine sulphate for the untoward effects of idiosyncrasy on excessive dosage of phenobarbital, thus permitting the drug to be continued. It is probable that in the future convulsive phenomena will be best managed by starting patients on phenobarbital and maintaining them on this if satisfactory relief can be secured on sub-toxic doses and that if, by the addition of amphetamine sulphate, satisfactory relief can be maintained, the patient will be kept on this regimen. Those showing stupor, drowsiness, loss of energy, or failure to respond to the drug will then be tried on dilantin or a combination of these two drugs. No general statement can be made regarding dosage of drugs and each case must be individualized.

Numerous minor toxic effects, including tremors, ataxia, and dizziness, have been observed in some 15 % of cases by Merritt and Putnam.<sup>40b</sup> A toxic dermatitis occurred in 5 % of all their cases and non-thrombocytopenic purpura in one patient. The same authors<sup>40c</sup> later report that an overdosage of the drug may produce drowsiness, ataxia, nystagmus, and diplopia. An erythematous morbilliform scarlatinaform rash appeared in 5 % of all their cases and one patient developed a mild exfoliative dermatitis accompanied by fever and eosinophilia. Kimball and Horan<sup>26</sup> found that 10 % of all children developed skin rash during the second week of therapy; 51 % of all cases showed various degrees of hyperplasia of the gums. The changes, however, were not characteristic of scurvy since the gums were firm and did not bleed. He felt that vitamin C metabolism was involved and the cases improved upon being so treated. Even without treatment the gums returned to normal if dilantin was stopped for as long as 3 months. He reports a

death in one patient taking dilantin due to gastritis with hemorrhage. The contention that these gum changes were due to deficiency of ascorbic acid was disproved by Gruhzt.<sup>18</sup>

Several instances have been reported in which delusions and hallucinations, excessive activity, and other psychic manifestations have resulted. Pratt<sup>47</sup> reports toxic reactions in 73% of 52 patients treated by him, the most common being subjective tremulousness with a feeling of apprehension and tension, tremors, burning sensation in the eyes, blurring of vision, diplopia, dizziness, ataxia, nausea, and sometimes vomiting. These usually occurred within 3 to 10 days after treatment was begun. Five psychotic states were encountered in association with treatment. Mild gum hyperplasia occurred in 50% of the cases. When any or all of the above toxic symptoms occur the medicine should be completely stopped or markedly reduced in amount temporarily and may be reinstated after a short period, usually without a recurrence of the symptoms. The patient should be maintained on whatever other available anti-convulsants there are at hand when the dilantin is stopped.

Coincident with the great mechanical, chemical, and theoretical advances that have come in the last few years in the field of convulsive disorder there is danger of a concomitant failure to remember that in the end we are treating patients and not convulsions. This fact was recognized by Jackson<sup>22</sup> in 1855, reiterated by Clark, in 1922, and ably emphasized by Cobb<sup>4</sup> this year. Social corrective, social constructive, psychiatric interviews and psychoanalytic therapies are considered by him as an essential part of the therapy of any epileptic patient. Such of these as are needed are supplied by the physician. In many of his cases he has been able to secure complete cessation of epileptic phenomena without or upon minimal doses of chemical substances by adhering to this policy. Wilson<sup>55</sup> has likewise emphasized the necessity of treating the patient and his environment if one is to discharge the obligations of a physician to an individual with any type of convulsive disorder.

FRANKLIN G. EBAUGH, M.D.

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## PHYSIOLOGY

### PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 16, 1940

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The Effect of Tobacco Smoke and Nicotine Upon the Normal Heart and in the Presence of Myocardial Disease Produced by Coronary Artery Ligation: an Experimental Study in Dogs. SAMUEL BELLET, RICHARD H. MEADE, JR., ALFRED KERSHBAUM, and LEON SCHWARTZ (Department of Surgical Research and Robinette Foundation, University of Pennsylvania, and Philadelphia General Hospital). The object of these experiments was to determine whether or not a difference in tolerance to tobacco smoke and nicotine exists in the normal heart as compared to hearts where myocardial damage was produced by coronary artery ligation. The unanesthetized dog was used in all experiments. The effects of inhalation of tobacco smoke and nicotine in various doses on the electrocardiogram of the normal dog was first



determined. Myocardial damage was then produced by ligation of the anterior descending branch of the left coronary artery and its accompanying vein. Such a preparation presents the opportunity for studying the effects of nicotine in the presence of acute infarction (1 to 4 days), subacute infarction (5 to 11 days) and chronic infarction (after 18 days). Following the inhalation of tobacco smoke, considerable variation in the electrocardiographic effects were observed at different times in the same animal. This was apparently the result of differences in absorption because of variations in the depth of inspiration. Since nicotine is the chief ingredient responsible for the toxic effects of tobacco smoke and in order that the amount absorbed could be definitely controlled, nicotine injected intramuscularly was used in our later experiments. It was found that the electrocardiographic changes were identical to those produced by inhalation of tobacco smoke. The electrocardiographic effects were graded as slight, moderate and severe, depending on the *T* wave changes and the characteristics and duration of the resulting arrhythmias.

It was found that normal animals were able to receive doses from 0.2 to 0.8 mg./kilo with development of relatively slight electrocardiographic effects. Following coronary ligation, severe effects were observed with a dose of 0.2 mg./kilo in most of the animals in the acute stage. These effects became less marked as the chronic stage of infarction was reached. However, the effects were more marked in the chronic stage than in the normal control. A parallel apparently existed between the severity of the electrocardiographic effects and the grade of myocardial disease.

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**The Action of Quinine Methochloride and  $\beta$  Erythroidine in Human Subjects and a Method for its Quantitative Determination.** A. M. HARVEY, R. L. MASLAND, and R. S. WIGTON (Eldridge Reeves Johnson Research Foundation and the Institute of Neurology, University of Pennsylvania). A new method has been developed by which the action of drugs on neuromuscular function can be studied quantitatively. It consists in recording the action potential of an entire muscle during maximal stimulation of its motor nerve.

Recording electrodes are placed on the skin over the tendon and belly of the abductor digiti quinti muscle, and the ulnar nerve is maximally stimulated, above the elbow, by means of condenser discharges. The resulting muscle action potential is the summation of the action potentials of all the individual fibers, and its size is proportional to the number of fibers contracting. Changes in its size during the administration of a curarizing substance are proportional to the degree of neuromuscular block effected.

The curare-like effect of a given dose of either quinine methochloride or  $\beta$  erythroidine depends largely on the rate of injection, as both are rather rapidly destroyed, and their action is of short duration. During injection there develops first ptosis and weakness of the extrinsic ocular muscles. At this time there is little obvious weakness of the somatic muscles, but when the ulnar nerve is stimulated repetitively, the successive action potentials of the muscle show an exponential decline in

size. A single response is reduced in amplitude and is followed by a long period of depression lasting over two seconds.

The changes in myasthenia gravis have been found to be entirely similar to those produced by partial curarization in the human subject.

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**A Method for the Measurement of Intra-intestinal Pressure and its Clinical Significance.** W. O. ABBOTT, H. K. HARTLINE, J. P. HERVEY, F. J. INGELFINGER, A. J. RAWSON and L. ZETZEL (Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, and the Johnson Foundation of Medical Physics, Hospital of the University of Pennsylvania). A method has been devised for measuring the pressure in the human alimentary tract simultaneously at several points along its length. Small metal capsules, each containing a flexible diaphragm, are attached at suitable intervals to a rubber tube, which is then swallowed by the subject. The diaphragm of each capsule carries an electric contact arranged to close when the pressure inside the rubber tube has been adjusted to equality with the pressure outside the capsule. The pressures necessary to close the circuits to the various capsules are determined automatically at intervals of 2 seconds and recorded on a slowly moving paper, giving essentially continuous traces of the pressures in the gut at the locations of each of the capsules.

This method has proved to be clinically practical. It is no more trying to a patient than a duodenal drainage. It is particularly adapted to the study of the full rather than the fasting digestive tract. When used in conjunction with fluoroscopy it makes possible a correlation of the movement of contents with the pressures causing the movement. Ordinarily a basal "tonus pressure" is easily detectable in the gut lumen with waves of variable amplitude superimposed upon it. In the upper small intestine tonus pressures of 11 to 15 cm. H<sub>2</sub>O are commonly seen with rises to 20 or 30 cm. as waves pass, and occasionally even to momentary peaks of 50 or 60 cm. The waves and the tonus level may vary independently. The results obtained so far suggest that a valuable insight into the mechanism of symptom production and the effects of treatment may develop from the application of this method.

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**The Mechanism of the Storage of Iodine in the Thyroid and the Passage of the Thyroid Hormone to the Tissues.\*** J. F. McCLENDON, W. C. FOSTER and W. G. KIRKLAND (Department of Physiology, Hahnemann Medical College). Goiter occurs in all parts of the world but varies inversely with the distribution of iodine.† In very goitrous countries congenital goiter is the rule and congenital weakness is one of the signs of cretinism just as it is in animals. Goiter may be produced in animals by lack of iodine in the diet. Goiter varies inversely with the iodine content of cabbage as well as of other foods. Although thyroxine is the active ingredient of the thyroid hormone, thyroglobulin (of molecular weight 700,000) without iodine is formed first and the tyrosine is partially changed to thyroxine. The tyrosine + diiodo-tyrosine + thyroxine content of thyroglobulin (calculated as tyrosine) remains constant

\* Aided by a grant from the Elizabeth Thompson Science Fund, Boston.

† McCleendon, J. F.: Iodine and the Incidence of Goiter, Univ. of Minnesota Press, 1939.

at 3.4 % whereas the thyroxine content varies from an average of 0.32 % for "normal" to 0.02 % for goiters not subjected to iodine medication. Thyroglobulin was forced out between cells by centrifugal force of 200,000 times gravity.

The thyroxine + thyroglobulin-iodine content of blood and tissues was determined by powdering the tissue, extracting with methanol and acetone and analyzing the residual iodine by a platinum combustion tube, electrometric method. Added thyroxine and thyroglobulin were recovered but added diiodotyrosine and potassium iodide were completely removed by the extraction.

From a study of the blood and basal metabolic rates of 333 patients and of tissues of numerous autopsies, we have found that for every microgram of thyroxine iodine in 100 cc. of blood there is about 1 mg. of thyroxine in the body of the adult. These values are related to the metabolic rate in percentage of normal averages as follows (correlation coefficient +0.627):

Basal metabolic rate . . .	-30	-20	-10	0	+10	+20	+30	+40	+50
Micrograms thyroxine iodine in 100 cc. blood . . .	2	3	4	5	6	7	8	9	10
Milligrams thyroxine in body . . . . .	2	3	4	5	6	7	8	9	10

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